

NTP TECHNICAL REPORT
ON THE
TOXICOLOGY AND CARCINOGENESIS
STUDIES OF
PYRIDINE
(CAS NO. 110-86-1)
IN F344/N RATS, WISTAR RATS, AND B6C3F₁ MICE
(DRINKING WATER STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

March 2000

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: <http://ntp-server.niehs.nih.gov>.

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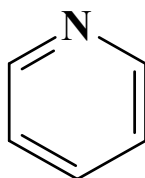
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ABSTRACT



PYRIDINE

CAS No. 110-86-1

Chemical Formula: C_5H_5N Molecular Weight: 79.10

Synonyms: Azabenzene, azine

Pyridine is used as a denaturant in alcohol and anti-freeze mixtures, as a solvent for paint, rubber, and polycarbonate resins, and as an intermediate in the manufacture of insecticides, herbicides, and fungicides. It is used in the production of piperidine, an intermediate in the manufacture of rubber and mepiquat chloride, and as an intermediate and solvent in the preparation of vitamins and drugs, dyes, textile water repellants, and flavoring agents in food. Pyridine was nominated for study because of its large production volume and its use in a variety of food, medical, and industrial products. Male and female F344/N rats, male Wistar rats, and male and female B6C3F₁ mice were exposed to pyridine (approximately 99% pure) in drinking water for 13 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, cultured Chinese hamster ovary cells, *Drosophila melanogaster*, and mouse bone marrow cells.

13-WEEK STUDY IN F344/N RATS

Groups of 10 male and 10 female F344/N rats were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 5, 10, 25, 55, or 90 mg pyridine/kg body weight). Two females exposed to 1,000 ppm

died during week 1. Final mean body weights of 1,000 ppm males and females and 500 ppm females were significantly less than controls. Water consumption by female rats exposed to 1,000 ppm was less than that by controls. At study termination, evidence of anemia persisted in the 500 and 1,000 ppm males and all exposed groups of females. There was evidence of hepatocellular injury and/or altered hepatic function demonstrated by increased serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations in 500 and 1,000 ppm rats. The estrous cycle length of 1,000 ppm females was significantly longer than that of the controls. Liver weights of males and females exposed to 250 ppm or greater were significantly greater than controls. In the liver, the incidences of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation were generally increased in 500 and 1,000 ppm males and females relative to controls. In the kidney, the incidences of granular casts and hyaline degeneration (hyaline droplets) were significantly increased in 1,000 ppm males and slightly increased in 500 ppm males; these lesions are consistent with α_2 -globulin nephropathy. Additionally, there were increased incidences and/or severities of protein casts, chronic inflammation, mineralization, and regeneration primarily in 500 and 1,000 ppm males.

13-WEEK STUDY IN MALE WISTAR RATS

Groups of 10 male Wistar rats were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 5, 10, 30, 60, or 100 mg/kg). One male rat exposed to 500 ppm died during week 1. Final mean body weights of rats exposed to 250, 500, or 1,000 ppm were significantly less than those of the controls. Water consumption by rats exposed to 1,000 ppm was lower than that by controls. There was evidence of hepatocellular injury and/or altered hepatic function in the 500 and 1,000 ppm groups, similar to that observed in the 13-week study in F344/N rats. Incidences of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation in the liver of rats exposed to 500 or 1,000 ppm were significantly increased relative to controls.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F₁ mice were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 10, 20, 50, 85, or 160 mg/kg for males and 10, 20, 60, 100, or 190 mg/kg for females). One female mouse exposed to 250 ppm died during week 2. Final mean body weights of female mice exposed to 1,000 ppm were significantly less than those of controls. Water consumption by exposed female mice was lower than that by controls at week 1 but generally slightly higher than controls at week 13. Sperm motility in exposed male mice was significantly decreased relative to controls. Liver weights were significantly increased relative to controls in males exposed to 100 ppm or greater and in 250 and 500 ppm females. No chemical-related lesions were observed in male or female mice.

2-YEAR STUDY IN F344/N RATS

Groups of 50 male and 50 female F344/N rats were exposed to pyridine in drinking water at concentrations of 0, 100, 200, or 400 ppm (equivalent to average daily doses of 7, 14, or 33 mg/kg) for 104 (males) or 105 (females) weeks.

Survival, Body Weights, and Water Consumption

Survival of exposed males and females was similar to that of controls. Mean body weights of 400 ppm males and females were generally less than those of the controls throughout the study, and those of 200 ppm males and females were less during the second year of the study. Water consumption by males and females exposed to 200 or 400 ppm was generally greater than that by controls.

Pathology Findings

Incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in male rats exposed to 400 ppm were significantly increased compared to controls and exceeded the historical control ranges. The findings from an extended evaluation (step section) of the kidneys did not reveal additional carcinomas, but additional adenomas were observed in each group of males. In the standard evaluation, an increased incidence of renal tubule hyperplasia was observed in 400 ppm males compared to controls. Incidences of mononuclear cell leukemia in female rats were significantly increased in the 200 and 400 ppm groups, and the incidence in the 400 ppm group exceeded the historical control range.

Exposure concentration-related nonneoplastic liver lesions were observed in males and females, and the incidences were generally increased in groups exposed to 400 ppm. These included centrilobular cytomegaly, cytoplasmic vacuolization, periportal fibrosis, fibrosis, centrilobular degeneration and necrosis, and pigmentation. Bile duct hyperplasia occurred more often in exposed females than in controls.

2-YEAR STUDY IN MALE WISTAR RATS

Groups of 50 male Wistar rats were exposed to pyridine in drinking water at concentrations of 0, 100, 200, or 400 ppm (equivalent to average daily doses of 8, 17, or 36 mg/kg) for 104 weeks.

Survival, Body Weights, and Water Consumption

Survival of rats exposed to 200 or 400 ppm was significantly less than that of the controls. Mean body

weights of rats exposed to 100, 200, or 400 ppm were significantly less than controls. Water consumption was similar by control and exposed rats.

Pathology Findings

The incidence of testicular interstitial cell adenoma in rats exposed to 400 ppm was significantly increased compared to controls. Incidences of interstitial cell hyperplasia were observed in control and exposed groups and were slightly, but not significantly, increased in rats exposed to 200 or 400 ppm.

Severity of nephropathy was marked in all groups, and additional evidence of kidney disease, including mineralization in the glandular stomach, parathyroid gland hyperplasia, and fibrous osteodystrophy, was observed in 100 and 200 ppm rats. The incidences of hepatic centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and/or pigmentation were increased in one or more exposed groups.

2-YEAR STUDY IN MICE

Groups of 50 male B6C3F₁ mice were exposed to pyridine in drinking water at concentrations of 0, 250, 500, or 1,000 ppm (equivalent to average daily doses of 35, 65, or 110 mg/kg) for 104 weeks, and groups of 50 female B6C3F₁ mice were exposed to pyridine in drinking water at concentrations of 0, 125, 250, or 500 ppm (equivalent to average daily doses of 15, 35, or 70 mg/kg) for 105 weeks.

Survival, Body Weights, and Water Consumption

Survival of exposed males and females was similar to that of the controls. Mean body weights of 250 and 500 ppm females were less than controls. Water consumption by males exposed to 250 or 500 ppm was generally greater than that by controls during the last year of the study; male mice exposed to 1,000 ppm consumed less water than controls throughout the study. Water consumption by exposed females was generally lower than that by controls during the first year of the study, but greater than controls during the second year.

Pathology Findings

Hepatocellular neoplasms, including hepatoblastomas, in exposed male and female mice were clearly related

to pyridine exposure. Additionally, many mice had multiple hepatocellular neoplasms. The incidences of hepatocellular neoplasms in exposed males and females generally exceeded the historical control ranges for drinking water studies. Neoplasms from control mice, 1,000 ppm males, and 500 ppm females were negative when stained for p53 protein.

GENETIC TOXICOLOGY

Pyridine was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 or in L5178Y mouse lymphoma cells, with or without S9 metabolic activation, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9. Pyridine was tested for induction of sex-linked recessive lethal mutations in adult male *Drosophila melanogaster*, and mixed results were obtained. In one experiment, administration by injection gave negative results, but feeding produced an equivocal response. A second experiment generated negative results by injection and feeding. A third experiment showed significant increases in sex-linked recessive lethal mutations in flies treated with pyridine by injection but not by feeding. Overall, results of the sex-linked recessive lethal mutations test in *Drosophila melanogaster* were considered negative by feeding and equivocal by injection. Results of a single reciprocal translocation test in male *Drosophila melanogaster* were negative. No induction of chromosomal aberrations or micronuclei was noted in bone marrow cells of male mice administered pyridine via intraperitoneal injection.

CONCLUSIONS

Under the conditions of these 2-year drinking water studies, there was *some evidence of carcinogenic activity** of pyridine in male F344/N rats based on increased incidences of renal tubule neoplasms. There was *equivocal evidence of carcinogenic activity* of pyridine in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was *equivocal evidence of carcinogenic activity* in male Wistar rats based on an increased incidence of interstitial cell adenoma of the testis. There was *clear evidence of carcinogenic activity* of pyridine in male and female B6C3F₁ mice based on increased incidences of malignant hepatocellular neoplasms.

In F344/N rats, exposure to pyridine resulted in increased incidences of centrilobular cytomegaly and degeneration, cytoplasmic vacuolization, and pigmentation in the liver of males and females; periportal fibrosis, fibrosis, and centrilobular necrosis in the liver of males; and bile duct hyperplasia in females. In male

Wistar rats, pyridine exposure resulted in increased incidences of centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation in the liver, and, secondary to kidney disease, mineralization in the glandular stomach and parathyroid gland hyperplasia.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 15.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pyridine

| | Male F344/N Rats | Female F344/N Rats | Male Wistar Rats | Male B6C3F ₁ Mice | Female B6C3F ₁ Mice |
|---|--|---|--|--|--|
| Concentrations in drinking water | 0, 100, 200, or 400 ppm | 0, 100, 200, or 400 ppm | 0, 100, 200, or 400 ppm | 0, 250, 500, or 1,000 ppm | 0, 125, 250, or 500 ppm |
| Body weights | 200 and 400 ppm groups less than control group | 200 and 400 ppm groups less than control group | Exposed groups less than control group | Exposed groups similar to control group | Exposed groups less than control group |
| Survival rates | 25/50, 20/50, 25/50, 16/50 | 32/50, 37/50, 29/50, 26/50 | 22/50, 14/50, 11/50, 7/50 | 35/50, 28/50, 35/49, 35/50 | 32/50, 30/50, 22/50, 29/50 |
| Nonneoplastic effects | <u>Liver:</u> centrilobular cytomegaly (0/50, 4/49, 8/50, 6/50); cytoplasmic vacuolization (4/50, 6/49, 13/50, 17/50); periportal fibrosis (0/50, 0/49, 2/50, 29/50); fibrosis (1/50, 1/49, 1/50, 10/50); centrilobular degeneration (1/50, 3/49, 2/50, 8/50); centrilobular necrosis (0/50, 3/49, 0/50, 5/50); pigmentation (4/50, 11/49, 20/50, 25/50) | <u>Liver:</u> centrilobular cytomegaly (0/50, 1/50, 4/50, 20/50); cytoplasmic vacuolization (10/50, 7/50, 9/50, 18/50); centrilobular degeneration (1/50, 2/50, 2/50, 7/50); bile duct hyperplasia (20/50, 29/50, 34/50, 29/50); pigmentation (6/50, 2/50, 6/50, 17/50) | <u>Liver:</u> centrilobular degeneration (1/50, 15/50, 25/50, 33/50); centrilobular necrosis (5/50, 6/50, 4/50, 23/50); fibrosis (1/50, 5/50, 26/50, 31/50); periportal fibrosis (0/50, 0/50, 5/50, 7/50); pigmentation (6/50, 15/50, 34/50, 42/50) <u>Glandular Stomach:</u> mineralization (8/49, 25/50, 16/48, 6/48) <u>Parathyroid Gland:</u> hyperplasia (16/48, 32/47, 29/48, 12/47) | None | None |
| Neoplastic effects | <u>Kidney:</u> renal tubule adenoma (standard evaluation - 1/50, 0/48, 2/50, 6/49; standard and extended evaluations combined- 2/50, 3/48, 6/50, 10/49); renal tubule adenoma or carcinoma (standard evaluation - 1/50, 1/48, 2/50, 6/49; standard and extended evaluations combined- 2/50, 4/48, 6/50, 10/49) | None | None | <u>Liver:</u> hepatocellular adenoma (29/50, 40/50, 34/49, 39/50); hepatocellular carcinoma (15/50, 35/50, 41/49, 40/50); hepatoblastoma (2/50, 18/50, 22/49, 15/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (38/50, 47/50, 46/49, 47/50) | <u>Liver:</u> hepatocellular adenoma (37/49, 39/50, 43/50, 34/50); hepatocellular carcinoma (13/49, 23/50, 33/50, 41/50); hepatoblastoma (1/49, 2/50, 9/50, 16/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (41/49, 42/50, 45/50, 44/50) |
| Uncertain findings | None | <u>Mononuclear cell leukemia:</u> (12/50, 16/50, 22/50, 23/50) | <u>Testis:</u> interstitial cell adenoma (5/50, 6/49, 4/49, 12/50) | None | None |
| Level of evidence of carcinogenic activity | Some evidence | Equivocal evidence | Equivocal evidence | Clear evidence | Clear evidence |

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pyridine

Genetic toxicology

| | |
|--|--|
| <i>Salmonella typhimurium</i> gene mutations: | Negative in strains TA98, TA100, TA1535, and TA1537, with and without S9 |
| Mouse lymphoma gene mutations: | Negative with and without S9 |
| Sister chromatid exchanges | |
| Cultured Chinese hamster ovary cells <i>in vitro</i> : | Negative with and without S9 |
| Chromosomal aberrations | |
| Cultured Chinese hamster ovary cells <i>in vitro</i> : | Negative with and without S9 |
| Mouse bone marrow <i>in vivo</i> : | Negative |
| Sex-linked recessive lethal mutations | |
| <i>Drosophila melanogaster</i> : | Equivocal by injection; negative by feeding |
| Reciprocal translocations | |
| <i>Drosophila melanogaster</i> : | Negative |
| Micronucleated erythrocytes | |
| Mouse bone marrow <i>in vivo</i> : | Negative |

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on pyridine on 10 December 1997 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 10 December 1997, the draft Technical Report on the toxicology and carcinogenesis studies of pyridine received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of pyridine by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on any survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions for the 2-year studies were *some evidence of carcinogenic activity* in male F344/N rats, *equivocal evidence of carcinogenic activity* in female F344/N rats and male Wistar rats, and *clear evidence of carcinogenic activity* in male and female B6C3F₁ mice.

Dr. Cullen, a principal reviewer, agreed with the proposed conclusions. He noted the large amount of inflammation in mouse livers and asked whether they had been screened for the possible presence of *Helicobacter hepaticus* infection. Dr. J.R. Hailey, NIEHS, said there was no frozen tissue available to perform PCR-based assays for identification of *H. hepaticus*. However, the liver lesions observed were not consistent with those typically associated with *H. hepaticus* infection.

Dr. Fischer, the second principal reviewer, agreed with the conclusions. She said the discussion should include comments on increased incidences of metastatic neoplasms in mice compared to rats. Dr. Dunnick agreed. Dr. Fischer expressed concern that the Wistar rats exposed to 400 ppm did not live long enough to produce neoplasms, and, thus, this experiment was not informative.

Dr. Bus, the third principal reviewer, did not agree with the proposed conclusions for female rats and mice and for male Wistar rats. He said the proposed conclusion of equivocal evidence in female rats was not warranted based on the lack of dose response, incidence values that only slightly exceeded recent NTP historical

control values, and excessive body weight depressions that confound interpretation of chemical-associated neoplasms. Dr. Dunnick responded that by definition, the increases in the incidences of mononuclear cell leukemia were uncertain findings. With regard to male Wistar rats, Dr. Bus stated that the severe toxicity associated with markedly decreased survival and effects on body weight gain, especially at 200 and 400 ppm, compromised interpretation of the increased incidence of testicular adenomas in the 400 ppm group. Finally, he thought it difficult to understand a conclusion of clear evidence in female mice in view of the profound body weight loss over the last 25 weeks of the study, and though there was an exposure-related increase in the incidences of malignant liver neoplasms, liver adenomas and total neoplasms were not altered. Dr. Dunnick said the level of clear evidence was justified by the large exposure-related increased incidences of malignant neoplasms. The body weight loss was due in part to the development of liver neoplasms. Dr. J.K. Haseman, NIEHS, noted that while the incidence of liver neoplasms in control female mice may have been one of the highest seen in the NTP, almost all neoplasms were adenomas. On the other hand, almost every exposed animal that lived one year or longer developed a liver neoplasm, often multiple neoplasms, and often carcinomas or hepatoblastomas, with many neoplasms metastasizing to the lung, constituting one of the strongest carcinogenic effects ever seen at this site in his experience. Dr. Bus said this changed his perspective on the neoplasms in female mice.

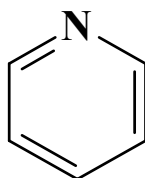
Further discussion of whether hepatoblastomas should be viewed and weighed separately from hepatocellular carcinomas ensued. Dr. Hailey thought they should be viewed as part of a natural progression and that with chemicals having neoplasm promoter activity there is almost always an associated increase in hepatoblastomas. There was discussion about the appropriateness in general of combining benign and malignant neoplasms. Dr. J. Russo argued that combining can be misleading. Dr. Hailey commented that with some neoplasm types combining might be controversial but with the liver (mice) and the kidney (rats), the sites at issue here, there is a spectrum of lesions from foci or hyperplasia to adenoma to carcinoma that represents a

morphological and biological continuum, and combining seems appropriate. Dr. Bailer said that, based on the data in the report, he would have considered clear evidence as the proposed conclusion for male rats. Dr. Bucher observed that NTP is using its combined experience to delineate between some evidence and clear evidence based on its historical perspective.

Dr. Bus moved that the Technical Report on pyridine be accepted with the revisions discussed and the conclusions as written for male F344/N rats, *some evidence of carcinogenic activity*, and for male and female B6C3F₁ mice, *clear evidence of carcinogenic activity*. He moved that the conclusions for female

F344/N rats and male Wistar rats be changed from *equivocal evidence of carcinogenic activity* to *inadequate study of carcinogenic activity*. Dr. Cullen seconded the motion. Dr. Haseman said that *inadequate study* is a category of evidence generally used only when there is some major flaw that makes the study uninterpretable. Dr. Bailer moved to amend the motion to keep the level of evidence for female F344/N rats and male Wistar rats as originally proposed, *equivocal evidence of carcinogenic activity*. Dr. Cullen seconded the amendment, which was accepted by six yes votes to one no vote (Dr. Bus). Dr. Bus's motion as amended by Dr. Bailer was accepted unanimously with seven votes.

INTRODUCTION



PYRIDINE

CAS No. 110-86-1

Chemical Formula: C_5H_5N Molecular Weight: 79.10

Synonyms: Azabenzene, azine

CHEMICAL AND PHYSICAL PROPERTIES

Pyridine is a slightly yellow or colorless, hygroscopic liquid with a characteristic nauseating odor and a burning taste. It is miscible with water, alcohols, diethyl ether, benzene, ligroin, and fatty oils and is slightly alkaline in reaction (pK_a of 5.19). Pyridine boils at approximately 115 °C at 760 mm Hg and has a specific gravity of 0.982, a vapor pressure of approximately 20 torr at 25 °C, and a vapor density of 2.73 (Jori *et al.*, 1983; *Hawley's*, 1987; *Merck Index*, 1989; Lewis, 1993). The liquid has a flash point (closed cup) of 20 °C and is flammable when exposed to heat, flame, or oxidizers; the vapor explodes upon contact with a flame or spark. When heated to decomposition, it emits cyanide fumes (*Hawley's*, 1987; Sittig, 1991; Lewis, 1993).

PRODUCTION, USE, AND HUMAN EXPOSURE

Pyridine is produced by coal carbonization and recovery from coke-oven gases and coal tar middle oil. Since the 1950s it has also been produced synthetically from the vapor phase reaction of acetaldehyde and ammonia, with formaldehyde and methanol sometimes added (Jori *et al.*, 1983; NCI, 1985).

Pyridine is a solvent that is widely employed in industry and the laboratory. It is used as a denaturant in alcohol and antifreeze mixtures, as a solvent for paint, rubber, and polycarbonate resins, and as an intermediate in the manufacture of insecticides (chlorpyrifos), herbicides (paraquat and trichloropyr), and fungicides. It is used in the production of piperidine, an intermediate in the manufacture of rubber and mepiquat chloride. Pyridine is also used as an intermediate and solvent in the preparation of vitamins and drugs, dyes, textile water repellants, and flavoring agents in food (NCI, 1985; *Hawley's*, 1987; ATSDR, 1992).

Manufacturers and consumers used an estimated 300,000 kg pyridine in 1977. Approximately 4.5 to 8.9×10^6 kg pyridine was produced in the United States in 1975, 27×10^6 kg in 1976, and 11.6×10^6 kg in 1978 (Pyridine Task Force, correspondence from Chairmen to U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC, 1978). No information on the current annual production of pyridine is available in the literature (ATSDR, 1992).

The greatest potential for exposure to pyridine is in the workplace. Occupational exposures, usually by inhalation or dermal absorption, may occur during pyridine

production or its use as a chemical intermediate or solvent (NCI, 1985). Exposure may also occur at coke-oven and oil-shale processing facilities. The U.S. Environmental Protection Agency (EPA) (1978) estimated that 249,000 persons were occupationally exposed to pyridine. The National Institute for Occupational Safety and Health (NIOSH) (1990) estimated the extent of potential human exposure between 1981 and 1983 at over 41,000 workers. The 8-hour, time-weighted average permissible exposure level for pyridine is 5 ppm (16 mg/m³) (ACGIH, 1997). NIOSH (1985) determined the concentration immediately dangerous to life or health to be 3,600 ppm. The pungent odor of pyridine (odor threshold of 0.17 ppm in air) serves to limit voluntary exposure (NCI, 1985). The odor becomes objectionable to unaccustomed individuals at 10 ppm, and olfactory fatigue occurs at greater than 5 ppm (Jori *et al.*, 1983).

Pyridine has rarely been detected in ambient air, water, or soil except near industrial sources (ATSDR, 1992). Pyridine is released into the atmosphere as fugitive emissions from coal gasification and oil shale processing facilities, from ironworking and coking plants (Masek, 1981), and from the combustion of polyisocyanate foam products (Seader *et al.*, 1972; Junk and Ford, 1980). The Agency for Toxic Substances and Disease Registry estimated that 298,438 pounds of pyridine were released in air, 4,630 pounds in surface water, and 303,650 pounds in groundwater in 1987; 209,880 pounds of pyridine were disposed of in publicly owned wastewater treatment plants (ATSDR, 1992). Pyridine has been identified in effluent from waste-water treatment plants (Ellis *et al.*, 1982), natural waters (Shelton and Hites, 1978), and groundwater near an underground coal gasification site (Stuermer *et al.*, 1982). An estimated 28,656 pounds of pyridine were released from industrial sources to land in 1987 (ATSDR, 1992). Many states have regulations concerning the acceptable ambient air concentrations of pyridine. For an 8-hour period, ambient air limits have been set at 300 µg/m³ in Connecticut, 150 µg/m³ in Indiana, 0.357 µg/m³ in Nevada, 0.3 µg/m³ in Tampa, Florida, and 0.15 µg/m³ in Vermont. Eighteen- and 24-hour limits have been set at 0.30 µg/m³ and 250 µg/m³ in North Dakota and Virginia, respectively, and annual limits have been set at 2.0 µg/m³ in New York and 35.7 µg/m³ in Kansas (NATICH, 1989).

In the United States, the general population may be exposed to low concentrations of pyridine by the inges-

tion of foods. Pyridine was detected among the natural volatile components of several foods, including fried chicken, cheese, and fried bacon (ATSDR, 1992). The EPA (1978) estimated the ingestion of pyridine in the United States to be about 500 mg per person per year. The FDA has approved the use of pyridine as a flavoring agent (21 CFR, § 172.515). Pyridine is also a coffee aroma constituent (ATSDR, 1992). Pyridine has been identified as a component of tobacco and marijuana smoke (Schmeltz and Hoffmann, 1977; Schumacher *et al.*, 1977; Meril *et al.*, 1981; Curvall *et al.*, 1984; Eatough *et al.*, 1989); the concentration of pyridine in indoor air contaminated with cigarette smoke may be as high as 16 µg/m³ (ATSDR, 1992).

REGULATORY STATUS

The EPA Office of Toxic Substances has included pyridine in its toxic chemical release reporting rule (40 CFR, Part 372), its health and safety data reporting rule (40 CFR, § 716.120), and its preliminary assessment information reporting rule (40 CFR, § 712.30). The annual reportable quantity of pyridine release to the environment has been set at 1,000 pounds by the EPA Office of Emergency and Remedial Response (40 CFR, § 302.4). The EPA Office of Solid Wastes lists pyridine as a constituent of hazardous waste (40 CFR, Part 261), monitors its levels in groundwater (40 CFR, Part 264), and restricts its disposal on land (40 CFR, Part 268).

ENVIRONMENTAL IMPACT

Pyridine exists in the atmosphere as a vapor. Atmospheric pyridine may be slowly photodegraded by hydroxyl radicals in the troposphere; the estimated atmospheric lifetime is 23 to 46 days. A large fraction of the atmospheric pyridine vapor phase would tend to dissolve in water vapor (clouds and rain) due to its high water solubility. The magnitude of the Henry's law constant for aqueous solutions of pyridine indicates that much of the atmospheric pyridine is removed by precipitation and suggests that the pyridine in water does not volatilize readily into the atmosphere. The volatility and sorption of pyridine from water varies considerably and is pH dependent. The rate of removal of pyridine from unfiltered river water by biodegradation depends on the initial pyridine concentration. At concentrations less than 20 mg/L, pyridine degradation was virtually complete in 8 days or less. Pyridine in

water may partition to soils and sediments to an extent that depends on the pH of the water and the organic carbon content of the soil. Due to its low carbon/water partition coefficient, pyridine is highly mobile in soil. In laboratory screening tests, however, 94% to 100% of the pyridine added to municipal wastewater biodegraded in 2 to 21 days (ATSDR, 1992).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Pyridine is absorbed by inhalation and by oral or dermal exposure. Pyridine is eliminated in exhaled air, feces, and urine as free base and/or metabolites (Jori *et al.*, 1983; NCI, 1985).

Pyridine is metabolized primarily by N-methylation and/or aromatic hydroxylation; urinary excretion of

metabolites and unchanged compound is the major route of elimination (NCI, 1985). The metabolic pathway in Figure 1 incorporates all the major urinary metabolites of pyridine that have been identified (ATSDR, 1992).

Experimental Animals

In a series of studies on pyridine N-methylation by D'Souza *et al.* (1980), a single dose of [^{14}C]-pyridine (7 mg/kg) was administered by intraperitoneal injection to groups of one to five female Wistar albino rats, female Tuck mice, male and female Dunkin-Hartley guinea pigs, female gerbils, female golden Syrian hamsters, male and female New Zealand White rabbits, and mongrel female cats. In the rat, mouse, guinea pig, gerbil, and hamster, 48% to 67% of the administered radiolabel was recovered in the urine within 24 hours. In both the cat and rabbit, 75% and 77% of the

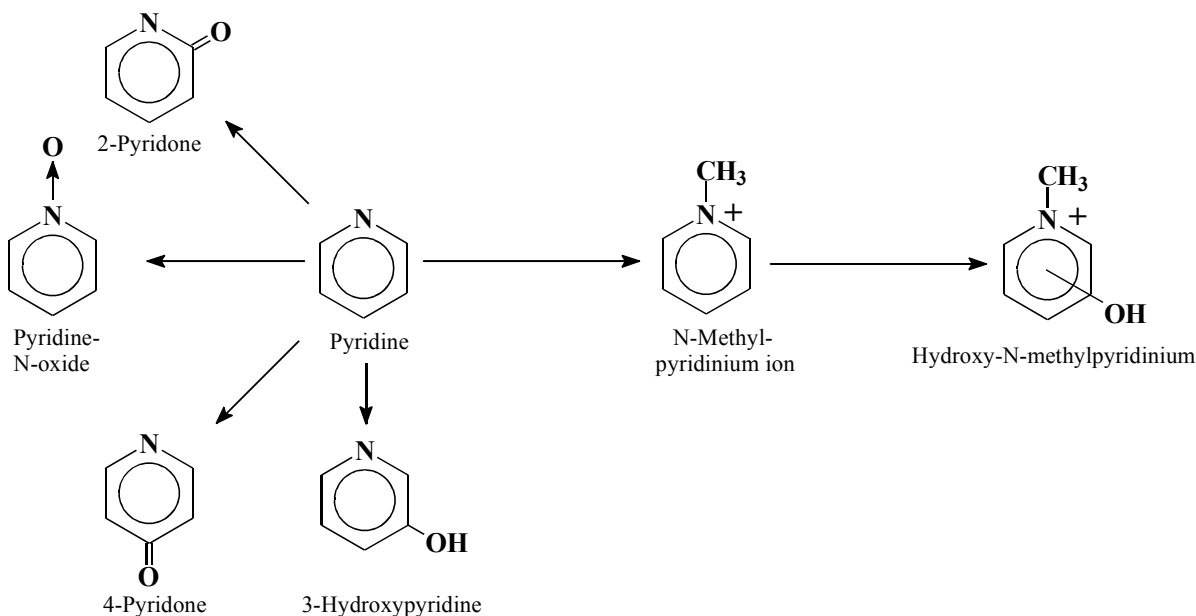


FIGURE 1
Proposed Metabolic Pathway for Pyridine (ATSDR, 1992)

administered radiolabel were recovered at 48 and 72 hours, respectively. Pyridine N-methylation was extensive (15% to 40% of the administered dose) in the guinea pig, gerbil, hamster, rabbit, and cat, and lower (approximately 5% to 12%) in the rat and mouse. To determine whether the N-methylpyridinium ion formed during the metabolism of pyridine is further metabolized, groups of three female rats and guinea pigs were injected intraperitoneally with 8 mg/kg N-methyl[2,6- ^{14}C]-pyridinium as an aqueous solution of the iodide. Greater than 95% of the radiolabel recovered in the urine was unchanged compound, indicating that N-methylpyridinium is largely metabolically stable (D'Souza *et al.*, 1980).

The effects of route of administration, dose, and methionine supplementation on the N-methylation of pyridine were also investigated by D'Souza *et al.* (1980) in the rat (a poor pyridine methylator) and guinea pig (a good pyridine methylator). [^{14}C]-Pyridine was administered orally at doses of 7, 68, or 357 mg/kg or intraperitoneally at doses of 1, 7, or 500 mg/kg to groups of three animals. N-Methylation of pyridine was found to be independent of the route of administration but dependent on the dose. In rats given 7 mg/kg [^{14}C]-pyridine orally, 58% of the total ^{14}C was excreted within 24 hours, with 3.1% of the dose as the N-methylpyridinium ion; 48% of the total ^{14}C was excreted within 24 hours following intraperitoneal injection of 7 mg/kg, with 5.0% of the dose as N-methylpyridinium ion. In the guinea pig, 31% of the administered dose was recovered in the urine as the N-methylpyridinium ion, regardless of the route of administration (recovery of orally and intraperitoneally administered total ^{14}C was 76% and 66%, respectively). In contrast, a study by Okuda (1959) demonstrated that 2.5 times more N-methylpyridine was produced following subcutaneous administration than following oral administration of pyridine to dogs.

For both the rat and guinea pig (D'Souza *et al.*, 1980), overall urinary recovery of ^{14}C was inversely proportional to the dose. The metabolic reaction was saturable in both species. In another experiment (D'Souza *et al.*, 1980), rats were pretreated with an injection of 1 g DL-methionine/kg 24 hours prior to administration of 7 mg [^{14}C]-pyridine/kg and then maintained on a diet enriched with DL-methionine. The excretion of total ^{14}C and N-methylpyridinium ion were unaffected by methionine supplementation, which demonstrated that low N-methylation in the rat is unrelated to a relative

deficiency of source methyl groups. In these same cross-species studies, Damani *et al.* (1982) identified 2-pyridine, 3-hydroxypyridine, and 4-pyridone in the urine of all species and pyridine N-oxide in all species except the rabbit, although the relative amounts of metabolites differed across species. In hamsters, guinea pigs, and cats, most of the urinary radioactivity was identified as unchanged pyridine and its C- and N-oxidized and N-methylated derivatives. A significant proportion of the excreted radioactivity in rats, gerbils, and rabbits could not be accounted for by the metabolites monitored in these studies, but 3-hydroxypyridine (not measured) was probably represented in the urine in a conjugated form. In rats, an unidentified cationic metabolite accounted for about 7.4% of the recovered radiolabel (Damani *et al.*, 1982).

D'Souza *et al.* (1980) suggested that N-methylation and quaternization of pyridine may result in the formation of a conjugation product (the N-methylpyridinium ion) more toxic than pyridine itself. The intraperitoneal LD₅₀ for N-methylpyridinium ion in mice is 0.22 g/kg, compared to 1.2 g/kg for pyridine. Production of N-oxides, generally associated with detoxification and increased elimination in several animal species and humans, may conceivably result in an increase in toxicity or carcinogenicity, and the N-oxidation of pyridine may represent a route for bioactivation (NCI, 1985; Kim *et al.*, 1991a).

Pyridine, which is metabolized by cytochromes P2E1 and P4B (CYP2E1 and CYP4B), enhances the expression of various hepatic P₄₅₀ isozymes in rats and rabbits (Kim and Novak, 1990; Kim *et al.*, 1991a, 1993; Nikula *et al.*, 1995). A series of studies demonstrated that pyridine enhances the expression of different gene subfamilies of rat hepatic cytochrome P₄₅₀ including CYP2E1, CYP1A1, CYP1A2, CYP2B1, and CYP2B2 (Kim and Novak, 1990; Kim *et al.*, 1991a,b; Hotchkiss *et al.*, 1993; Iba *et al.*, 1993; Agarwal *et al.*, 1994).

Pyridine caused a dose-dependent, 4- to 22-fold elevation of hepatic CYP2B1/2B2 over the intraperitoneal dosing regimen of 100 to 400 mg/kg per day in Sprague-Dawley rats. Pyridine treatment increased CYP2B1 and CYP2B2 poly (A)+ RNA levels approximately 69- and 34-fold, respectively, while CYP2E poly (A)+ levels failed to increase (Kim *et al.*, 1993). Pyridine is similar to phenobarbital (Lubet *et al.*, 1989) and oxazepam (Griffin *et al.*, 1995) in this induction of CYP2B enzymes. Lubet *et al.* (1989) have associated

the strength of this CYP2B induction response to the strength of liver neoplasm promotion in the rat, although the mechanisms are not known. Rice *et al.* (1994) have also studied the association between CYP2B induction and liver neoplasm-promoting activity in the rat, and while there is a correlation with an induction of CYP2B and liver neoplasm promotion (after initiation with N-nitrosodiethylamine), other factors may be involved. Chemicals such as phenobarbital, which induces cytochrome P₄₅₀s in the rodent liver, induce a wide variety of enzyme systems (referred to as pleiotropic response), and it is likely that several effects of the chemical play a role in its liver neoplasm-promoting ability (McClain, 1990).

Male Sprague-Dawley rats were given intraperitoneal doses of 2.5 mmol of pyridine or a metabolite (including pyridine-N-oxide, 2-hydroxypyridine, 3-hydroxypyridine, 4-hydroxypyridine, and pyridinium methyl iodide) per kg of body weight for 1 to 5 days and sacrificed after the final dose. Only pyridine and 2-hydroxypyridine caused hepatotoxicity as measured by increases in serum sorbitol dehydrogenase. Pyridine, pyridine-N-oxide, 3-hydroxypyridine, and 4-hydroxypyridine were all effective inducers of CYP2E1-mediated metabolism (Carlson, 1996). As an inducer of cytochrome P₄₅₀2E1 in both liver and lung, pyridine has been shown to affect the metabolism of xenobiotics including 2-butanol (Page and Carlson, 1993), ethyl carbamate (urethane) (Page and Carlson, 1994), and carbon tetrachloride (Day *et al.*, 1993) in various species including rat, mouse, and/or rabbit.

Humans

N-Methylpyridinium ion (5.5% and 12% of the dose) was present in urine collected 24 hours after two human volunteers received 3.4 mg [¹⁴C]-pyridine in orange juice (approximately 0.05 mg/kg) (D'Souza *et al.*, 1980). Pyridine-N-oxide was identified as a metabolite in the urine sample, accounting for 32% of the administered dose (Damani *et al.*, 1982). Approximately 25% of the urinary metabolites were not identified.

Pyridine and a number of its derivatives have been shown to cause selective inhibition of thromboxane synthetase *in vitro* in fresh citrated human blood (Miyamoto *et al.*, 1980) and in a test system employing the microsomal fraction of human platelet microsomes (Tai *et al.*, 1980); thromboxane A₂ is a potent labile inducer of platelet aggregation and vascular constriction. The inhibitory potency of pyridine on thromb-

oxane synthetase in these systems was 60 μ M in blood and 270 μ M in platelet microsomes. In addition, pyridine (1.5 mM) inhibited the aggregation of human platelets induced by arachidonic acid or adenosine triphosphate (Tai *et al.*, 1980).

TOXICITY

Experimental Animals

Reported pyridine LD₅₀/LC₅₀ values for rats are 891 to 1,580 mg/kg (oral), 360 mg/kg (intravenous), 866 to 1,150 mg/kg (subcutaneous), and approximately 8,000 to 9,000 ppm for 1 hour (inhalation) (Vernot *et al.*, 1977; Jori *et al.*, 1983; ATSDR, 1992). LD₅₀ values for mice are 1,500 mg/kg (oral), 1,200 mg/kg (intraperitoneal), 420 mg/kg (intravenous), and 1,250 mg/kg (subcutaneous) (Jori *et al.*, 1983).

Pyridine has been reported to cause toxic effects in the liver and kidney in experimental animal model systems. Pyridine administration (oral gavage) to dogs has produced toxic effects in the liver and kidney (Jori *et al.*, 1983). Decreased glutamine concentration and increased ammonia excretion were observed in rats (age and strain not specified) exposed to pyridine vapors at a concentration of 5 to 10 mg/L for a single 40-minute exposure (ATSDR, 1992).

In a study in Sprague-Dawley rats (Anderson, 1987), pyridine was administered by gavage at 0, 0.24, 1, 10, 25, or 50 mg/kg per day in water for 90 consecutive days. No treatment-related deaths occurred during the study. Body weights relative to controls were significantly reduced in male rats in the 50 mg/kg per day group. Dose-related, mildly elevated serum cholesterol levels occurred in females at 25 and 50 mg/kg per day on days 30 and 90, and female rats that received 10 mg/kg or greater had significantly increased liver weights. Mild inflammatory hepatic lesions were seen in 70% of males and 20% of females in the 50 mg/kg groups; the incidence of inflammatory hepatic lesions was 10% in male and female control groups. Lesions included mixed peribiliary infiltrate, bile ductule proliferation, enlarged and vacuolated hepatocytes, and necrosis of hepatocytes. Liver lesions also occurred in the 10 and 25 mg/kg groups.

In a study in which rats were given subcutaneous injections of pyridine twice weekly for a year at doses of 3, 10, 30, or 100 mg/kg (Mason *et al.*, 1971),

survival rates and neoplasm incidences in pyridine-treated rats were similar to those in the controls. Mean body weights of the dosed groups ranged from 84% to 95% of those of the controls at the end of the study.

Inhalation of 5 or 444 ppm pyridine 6 hours per day for 4 days was associated with olfactory epithelial lesions in the nasal mucosa of male F344/N rats characterized by vacuolar degeneration of sustentacular cells, focal, marked attenuation of the epithelium, loss of sensory neurons, and intraepithelial luminal structures (Nikula and Lewis, 1994). These lesions were associated with induction of carboxylesterase (Nikula *et al.*, 1995).

Humans

There are no adequate studies on the toxicity of pyridine in humans. Several reports indicate that pyridine may be moderately toxic by the oral, dermal, intravenous, and inhalation routes. The chemical can cause skin irritation and severe eye damage (Sittig, 1991; Lewis, 1993).

In a review of the literature on pyridine, ATSDR (1992) reported the death of a man receiving pyridine as an intermittent medication for the treatment of epilepsy. The patient was also taking other medications (including phenobarbital), and it was not possible to attribute this death specifically to pyridine.

A 29-year-old man who accidentally swallowed ½ cup (approximately 125 mL) of pyridine experienced nausea, dizziness, abdominal pain, and lung congestion followed by death within 2 days (Jori *et al.*, 1983).

Inhalation is a primary route of exposure to pyridine, and mild symptoms of central nervous system injury may result from exposure to approximately 10 ppm (Jori *et al.*, 1983; NCI, 1985). Similar symptoms (headache, dizziness, insomnia, nausea, and anorexia) were reported in workers exposed to 125 ppm pyridine, 4 hours per day for 1 to 2 weeks (Jori *et al.*, 1983).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Injection of 10 or 20 mg pyridine into eggs caused muscular hypoplasia in 15% or 67% of chicks, respectively. The 20 mg dose induced defective beaks in 4.9% of the chicks and short or twisted necks in 1.1% (ATSDR, 1992). No information related to the repro-

ductive or developmental toxicity of pyridine in humans was found in a search of the available literature.

CARCINOGENICITY

No information related to the carcinogenicity of pyridine in experimental animals or humans was found in a search of the available literature.

GENETIC TOXICITY

Pyridine has been tested in a variety of *in vivo* and *in vitro* assays, and with few exceptions, results were negative. No mutation induction (Pai *et al.*, 1978) or growth inhibition due to DNA damage was noted in *Escherichia coli* after treatment with pyridine (Warren *et al.*, 1981; Riebe *et al.*, 1982). No increases in gene mutation frequencies were observed in a variety of *Salmonella typhimurium* strains exposed to pyridine in the presence or the absence of S9 activation enzymes (Florin *et al.*, 1980; Kawachi *et al.*, 1980; Warren *et al.*, 1981; Riebe *et al.*, 1982; Haworth *et al.*, 1983). Zimmermann *et al.* (1986) reported induction of aneuploidy in *S. cerevisiae* D61.M after treatment with up to 1.1% pyridine, presumably resulting from disruption of microtubule assembly processes. No significant increases in mutant frequencies were seen in L5178Y mouse lymphoma cell cultures after incubation with pyridine, with or without S9 activation (McGregor *et al.*, 1988). There are two published data sets from *Drosophila melanogaster* sex-linked recessive lethal assays with pyridine, and the results are mixed. Valencia *et al.* (1985) reported negative results when pyridine was administered to adult male flies by injection (7,000 ppm) and equivocal results when feeding (700 ppm) was used as the route of administration. Mason *et al.* (1992) reported negative results in a sex-linked recessive lethal assay from a feeding study (500 ppm) but positive results after injection of 4,300 ppm pyridine. This positive result with pyridine in the sex-linked recessive lethal assay was followed by a test for induction of reciprocal translocations in male *Drosophila*, and negative results were obtained in this assay (Mason *et al.*, 1992).

Cytogenetic investigations in mammalian test systems yielded negative results with pyridine for induction of chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster ovary cells,

tested in the absence of S9 activation enzymes (Abe and Sasaki, 1977; Ishidate and Odashima, 1977; Kawachi *et al.*, 1980). *In vivo*, no induction of micronuclei in mouse bone marrow cells (Harper *et al.*, 1984) or chromosomal aberrations in rat bone marrow cells was reported after treatment with pyridine.

There are little mutagenicity data for metabolites of pyridine. Pyridine-1-oxide was negative in bacterial tests for gene mutation induction (Voogd *et al.*, 1980) and growth inhibition due to DNA damage, and it did not produce growth inhibition secondary to DNA damage in *S. cerevisiae* (Nagao and Sugimura, 1972). These tests were conducted without S9. 3-Hydroxypyridine, another pyridine metabolite, did not cause gene reversion in *S. typhimurium*, with or without S9 (Florin *et al.*, 1980).

In summary, there appears to be little evidence to indicate that pyridine is mutagenic in standard short-term tests.

STUDY RATIONALE

Pyridine was tested by the National Toxicology Program because of the large amount produced and its use in a variety of industrial products. The oral route of administration was selected to evaluate the systemic effects of pyridine. Pyridine has been shown to increase the severity of leukemia in a transplant model for leukemia in male F344/N rats (Dieter *et al.*, 1989), and male Wistar rats were added to these studies in order to evaluate the effects of pyridine in a rat model with a low spontaneous incidence of mononuclear cell leukemia.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PYRIDINE

Pyridine was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (00103BV). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix K). Reports on analyses performed in support of the pyridine studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless liquid, was identified as pyridine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of lot 00103BV was determined by elemental analyses, Karl Fischer water analysis, functional group titration, and gas chromatography. Elemental analyses for hydrogen and nitrogen were in agreement with the theoretical values for pyridine; results for carbon were slightly low. Karl Fischer water analysis indicated $0.049\% \pm 0.003\%$ water. Functional group titration indicated a purity of $99.8\% \pm 0.6\%$. Two gas chromatography systems indicated one major peak and no impurities with as much as 0.1% of the major peak area. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using gas chromatography. To ensure stability, the bulk chemical was stored at 1 to 8 °C in amber glass bottles in the dark. Stability was monitored during the 13-week and 2-year studies using gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared as needed by mixing pyridine with deionized water (Table K1).

Stability studies of a 0.01 mg/mL formulation were performed by the analytical chemistry laboratory using high-performance liquid chromatography. The stability of the dose formulation was confirmed for at least 3 weeks when stored in the dark at room temperature.

Periodic analyses of the dose formulations of pyridine were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. For the 13-week studies, dose formulations were analyzed after preparation at the beginning, midpoint, and end of the studies (Table K2). During the 2-year studies, dose formulations were analyzed approximately every 6 to 10 weeks (Table K3). All dose formulations analyzed and used during the 13-week studies were within 10% of the target concentration. Of the dose formulations analyzed during the 2-year studies, 191 of 192 were within 10% of the target concentration. One formulation was 47% less than the target concentration; because records indicated that the proper amounts of pyridine and deionized water were used, it is possible that the wrong dose formulation was sampled for analysis. This dose formulation was remixed, and the remix was found to be within 10% of the target concentration. All animal room samples were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory during the 13-week studies agreed with the results obtained by the study laboratory (Table K4).

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to pyridine and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F₁ mice were obtained from Taconic Farms (Germantown, NY); male Wistar rats were obtained from Charles River Laboratories (Kingston, NY). On receipt, rats and mice were approximately 5 weeks old. Animals were quarantined

for 12 to 14 days and were 7 or 8 weeks old on the first day of the studies. Before initiation of the studies, five male and five female F344/N rats and mice and five male Wistar rats were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female sentinel F344/N rats and mice and five male sentinel Wistar rats using the protocols of the NTP Sentinel Animal Program (Appendix N).

Groups of 10 male and 10 female F344/N rats and B6C3F₁ mice and 10 male Wistar rats were given drinking water containing 0, 50, 100, 250, 500, or 1,000 ppm pyridine (core study). Groups of 10 male and 10 female F344/N rats and 10 male Wistar rats exposed to the same concentrations were designated as special study animals for hematology and clinical chemistry analyses. Feed and water were available *ad libitum*; fresh control or treated water was provided twice weekly. Rats were housed five per cage, and mice were housed individually. Clinical findings were recorded weekly for rats and mice. Water consumption was recorded twice weekly by cage for core study animals. The animals were weighed initially and weekly thereafter. Details of the study design and animal maintenance are summarized in Table 1.

Blood from the retroorbital sinus was collected from special study rats on days 5 and 20 and core study rats at study termination for hematology and clinical chemistry analyses. Erythrocyte, leukocyte, and platelet counts; hemoglobin concentration; hematocrit, mean cell volume; mean cell hemoglobin; and mean cell hemoglobin concentration were measured with a Sysmex TOA E-2500. Blood smears were stained with Wright/Giemsa; differential leukocyte counts were based on classifying a minimum of 100 cells. Reticulocyte counts were done on a smear prepared from whole blood, stained with new methylene blue N, and incubated at room temperature; 1,000 erythrocytes were counted and the percent reticulocytes was determined. Clinical chemistry analyses were performed on the Roche Cobas FARA automated centrifugal analyzer (Roche Diagnostic Systems, Inc., Montclair, NJ). The hematology and clinical chemistry parameters measured are listed in Table 1.

At the end of the 13-week studies, blood was collected from the retroorbital sinus of all rats and mice for plasma pyridine concentration measurements. Pilot

studies determined that samples could be collected between 8 a.m. and 10 a.m. The samples were taken in silicon-coated tubes which contained buffered sodium citrate. A plasma analysis procedure was developed and evaluated at the study laboratory for the analysis of plasma pyridine concentrations ranging from 0.063 to 100 µg/mL. Concentrations less than the experimental level of quantitation (0.063 µg/mL) should be considered approximations. Plasma samples were treated with sodium hydroxide and 3-methylpyridine, the internal standard. The samples were extracted with dichloromethane, then analyzed using gas chromatography with nitrogen-phosphorous detection. The gas chromatography was performed on a 20% Carbowax 20M-TPA on 80/100 Chromosorb column, with a nitrogen carrier gas at a flow rate of 30 mL/minute, and an oven temperature of 89 °C for 7 minutes, then to 170 °C at 20 °C per minute, with a 2-minute hold. Three standard curve ranges were used to encompass the 1,600-fold quantitation range. Results from these analyses for rats are presented in Appendix J. Analyses of the samples for mice were not considered adequate and these data are not reported.

At the end of the 13-week studies, samples were collected for sperm motility and vaginal cytology evaluations on F344/N rats and mice exposed to 0, 250, 500, or 1,000 ppm. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides, and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in

buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65 °C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all core study animals. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 µm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on control and 1,000 ppm animals, and target organs were examined to the no-effect level. Table 1 lists the tissues and organs routinely examined. α2u-Globulin immunohistochemistry, using a primary antibody from Hazleton Laboratories, was assayed on selected animals from each exposure group.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female F344/N rats and 50 male Wistar rats were given drinking water containing 0, 100, 200, or 400 ppm pyridine for 104 (males) or 105 (females) weeks. Groups of 50 male B6C3F₁ mice were exposed to 0, 250, 500, or 1,000 ppm pyridine in drinking water for 104 weeks, and groups of 50 female B6C3F₁ mice were exposed to 0, 125, 250, or 500 ppm pyridine in drinking water for 105 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F₁ mice were obtained from Taconic Farms (Germantown, NY), and male Wistar rats were obtained from Charles River Laboratories (Portage, MI) for use in the 2-year studies. Rats and mice were quarantined for 12 to 14 days before the beginning of the studies. Five male and five female F344/N rats and mice and five male Wistar rats were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 7 weeks old at the beginning of the studies. The health of the animals was monitored

during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix N).

Animal Maintenance

F344/N rats were housed five per cage, male Wistar rats were housed three per cage, and mice were housed individually. Feed and water were available *ad libitum*. Water consumption was measured weekly by cage for the first 13 weeks and every 4 weeks thereafter. Cages and racks were rotated every two weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix M.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded at 4-week intervals, and body weights were recorded at the start of the study, weekly for the first 13 weeks, every 4 weeks until week 92 (F344/N rats), week 88 (male Wistar rats), or week 96 (mice), and then once every 2 weeks until study termination.

A complete necropsy and microscopic examination were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. For extended evaluation of renal proliferative lesions in male rats, kidneys were step sectioned at 1-mm intervals, and four additional sections were obtained from each kidney. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year rat studies, a quality assessment pathologist evaluated slides from all tumors and all potential target

organs, which included the liver and kidney of male F344/N rats, the liver of female F344/N rats, and the liver, kidney, and testis of male Wistar rats. For the 2-year mouse studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the liver, nose, and spleen of male and female mice, the adrenal cortex and lung of male mice, and the ovary and pituitary gland of female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses

between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Pyridine

| 13-Week Studies | 2-Year Studies |
|--|---|
| Study Laboratory TSI Mason Research Institute (Worcester, MA) | TSI Mason Laboratories (Worcester, MA) |
| Strain and Species Rats: F344/N and Wistar Mice: B6C3F ₁ | Rats: F344/N and Wistar Mice: B6C3F ₁ |
| Animal Source F344/N rats: Taconic Farms (Germantown, NY) Wistar rats: Charles River Laboratories (Kingston, NY) Mice: Taconic Farms (Germantown, NY) | F344/N rats: Taconic Farms (Germantown, NY) Wistar rats: Charles River Laboratories (Portage, MI) Mice: Taconic Farms (Germantown, NY) |
| Time Held Before Studies F344/N rats: 14 days (males) or 12 days (females) Wistar rats: 13 days Mice: 13 days (males) or 14 days (females) | F344/N rats: 12 days (males) or 13 days (females) Wistar rats: 13 days Mice: 13 days (males) or 14 days (females) |
| Average Age When Studies Began 7 weeks, except special study F344/N rats at 8 weeks | 7 weeks |
| Date of First Exposure Core Studies: F344/N rats: 24 January (males) or 22 January (females) 1990 Wistar rats: 8 February 1990 Mice: 20 December (males) or 21 December (females) 1989 Special Studies: F344/N rats: 3 February (males) or 1 February (females) 1990 Wistar rats: 1 March 1990 | F344/N rats: 23 April (males) or 24 April (females) 1991 Wistar rats: 14 May 1991 Mice: 3 April (males) or 4 April (females) 1991 |
| Duration of Exposure 13 weeks (core study animals) 19 days (special study F344/N rats) 20 days (special study Wistar rats) | F344/N and Wistar rats: 104 weeks (males) or 105 weeks (females) Mice: 104 weeks (males) or 105 weeks (females) |
| Date of Last Exposure Core Studies: F344/N rats: 25 April (males) or 23 April (females) 1990 Wistar rats: 30 May 1990 Mice: 21 March (males) or 22 March (females) 1990 Special Studies: F344/N rats: 22 February (males) or 20 February (females) 1990 Wistar rats: 20 March 1990 | F344/N rats: 13 April (males) or 22 April (females) 1993 Wistar rats: 4 May 1993 Mice: 25 March (males) or 1 April (females) 1993 |
| Necropsy Dates F344/N rats: 25 April (males) or 23 April (females) 1990 Wistar rats: 30 May 1990 Mice: 21 March (males) or 22 March (females) 1990 | F344/N rats: 13 April (males) or 21-22 April (females) 1993 Wistar rats: 4 May 1993 Mice: 24-25 March (males) or 1 April (females) 1993 |
| Average Age at Necropsy 19 weeks (core study) | F344/N and Wistar rats: 110 weeks (males) or 111 weeks (females) Mice: 110 weeks (males) or 111 weeks (females) |
| Size of Study Groups F344/N rats and mice: 10 males and 10 females Wistar rats: 10 males | F344/N rats and mice: 50 males and 50 females Wistar rats: 50 males |

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Pyridine

| 13-Week Studies | 2-Year Studies |
|---|---|
| Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights. | Same as 13-week studies |
| Animals per Cage F344/N and Wistar rats: 5 Mice: 1 | F344/N rats: 5 Wistar rats: 3 Mice: 1 |
| Method of Animal Identification Tail tattoo | Tail tattoo |
| Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available <i>ad libitum</i> | Same as 13-week studies |
| Water Deionized water via glass water bottles with stainless steel sipper tubes, available <i>ad libitum</i> , changed twice per week | Same as 13-week studies |
| Cages See-Through Systems polycarbonate, solid bottom (Lab Products, Inc., Rochelle Park, NJ), changed twice per week (rats) or weekly (mice) | Same as 13-week studies, except changed three times per week for male rats |
| Bedding F344/N and Wistar rats: Sani Chips (P.J. Murphy Products Corp., Montville, NJ), changed twice per week Mice: Beta Chips (P.J. Murphy Products Corp., Montville, NJ), changed weekly | Heat-treated hardwood chips (P.J. Murphy Forest Products, Montville, NJ), changed three times per week (male rats), twice per week (female rats), or weekly (mice) |
| Cage Filters Nonwoven fiber (Snow Filtration, Cincinnati, OH), changed once every 2 weeks | Same as 13-week studies |
| Racks Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed once every 2 weeks | Same as 13-week studies |
| Animal Room Environment Temperature: 20.6 -23.9 °C (F344/N rats); 18.9 -23.3 °C (Wistar rats); 20.6 -24.4 °C (mice) Relative humidity: 31%-57% (F344/N rats); 35%-56% (Wistar rats); 26%-49% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour | Temperature: 19.4 -24.4 °C (F344/N rats); 18.9 -26.7 °C (Wistar rats); 20.0 -24.4 °C (mice) Relative humidity: 24%-71% (F344/N rats); 25%-78% (Wistar rats); 20%-65% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour |
| Exposure Concentrations 0, 50, 100, 250, 500, or 1,000 ppm | F344/N and Wistar rats: 0, 100, 200, or 400 ppm Mice: 0, 250, 500, or 1,000 ppm (males); 0, 125, 250, or 500 ppm (females) |

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Pyridine

| 13-Week Studies | 2-Year Studies |
|---|---|
| <p>Type and Frequency of Observation Observed twice daily; animals were weighed initially and weekly thereafter; clinical findings were recorded weekly. Water consumption was recorded twice per week by cage.</p> | <p>Observed twice daily; animals were weighed initially, weekly for the first 13 weeks, every 4 weeks until week 92 (F344/N rats), week 88 (Wistar rats), or week 96 (mice), and then once every 2 weeks; clinical findings were recorded at 4-week intervals. Water consumption was measured weekly by cage for the first 13 weeks and every 4 weeks thereafter.</p> |
| <p>Method of Sacrifice CO₂</p> | <p>70%:30% CO₂:O₂</p> |
| <p>Necropsy Necropsy performed on all core study animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.</p> | <p>Necropsy performed on all animals.</p> |
| <p>Clinical Pathology Blood was collected from the retroorbital sinus of special study rats on days 5 and 20 and of core study rats at the end of the study for hematology and clinical chemistry analyses. Hematology: hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, nucleated erythrocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials Clinical chemistry: urea nitrogen, creatinine, protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbital dehydrogenase, bile acids</p> | <p>None</p> |
| <p>Histopathology Complete histopathology was performed on 0 and 1,000 ppm animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone (with marrow), brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (with adjacent skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach, testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. The kidney of male rats and the liver of all rats were also examined in all other exposure groups.</p> | <p>Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone (with marrow), brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (with adjacent skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach, testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.</p> |
| <p>Sperm Motility and Vaginal Cytology At the end of the studies, sperm samples were collected from male F344/N rats and mice in the 0, 250, 500, and 1,000 ppm groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per gram testis, spermatid heads per testis, sperm count, epididymal sperm concentration, and epididymal sperm motility. The left cauda, epididymis, and testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from all females exposed to 0, 250, 500, or 1,000 ppm for vaginal cytology evaluations. The following parameters were evaluated: estrous cycle length and relative frequency of estrous stages.</p> | <p>None</p> |
| <p>Determinations of Pyridine in Plasma At the end of the 13-week studies, blood was collected from the retroorbital sinus of all rats just before sacrifice for plasma pyridine concentration measurements.</p> | <p>None</p> |

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or removed from study for other reasons were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, C1, C4, D1, D5, E1, and E5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, D3, and E3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, D3, and E3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate

more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of $k=3$ was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F₁ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected tests were used in the analysis of lesion incidence, and reported P values are one sided. Values of P greater than 0.5 are presented as 1 P with the letter N added to indicate a lower incidence or negative trend in neoplasm occurrence relative to the control group (e.g., $P=0.99$ is presented as $P=0.01N$).

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972).

Hematology, clinical chemistry, plasma concentration, urinalysis, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison

methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of pyridine was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, mutations in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster*, and increases in the frequency of micronucleated erythrocytes in bone marrow of mice. The protocols for these studies and the results are given in Appendix F.

The genetic toxicity studies of pyridine are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the molecular structure and the effects of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical mutagenesis and the somatic mutation theory of cancer (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood

micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, because of the theoretical and observed associations between induced genetic damage and adverse effects in

somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

RESULTS

F344/N RATS 13-WEEK STUDY

Two females exposed to 1,000 ppm died during week 1; all other F344/N rats survived until the end of the study (Table 2). Final mean body weights of 1,000 ppm males and 500 and 1,000 ppm females and mean body weight gains of males and females exposed to 500 or 1,000 ppm were significantly less than those of the controls. Water consumption by female rats exposed to 1,000 ppm was less than that by the controls at week 1. Drinking water concentrations of 50, 100,

250, 500, or 1,000 ppm pyridine resulted in average daily doses of 5, 10, 25, 55, or 90 mg pyridine/kg body weight. There were no exposure-related clinical findings.

The hematology and clinical chemistry data for F344/N rats are listed in Table G1. On day 5, an erythrocytosis, demonstrated by increased hematocrit values, hemoglobin concentrations, and erythrocyte counts relative to controls, occurred in males exposed to 100 ppm or greater. An erythrocytosis would be consistent with dehydration, which can cause a relative erythrocytosis

TABLE 2
Survival, Body Weights, and Water Consumption of F344/N Rats in the 13-Week Drinking Water Study of Pyridine

| Concentration (ppm) | Survival ^a | Mean Body Weight ^b (g) | | | Final Weight Relative to Controls (%) | Water Consumption ^c | |
|------------------------|-----------------------|-----------------------------------|-----------|-----------|--|-----------------------------------|---------|
| | | Initial | Final | Change | | Week 1 | Week 13 |
| Male | | | | | | | |
| 0 | 10/10 | 149 ± 4 | 346 ± 9 | 197 ± 6 | | 132 | 78 |
| 50 | 10/10 | 145 ± 4 | 345 ± 7 | 201 ± 5 | 100 | 138 | 76 |
| 100 | 10/10 | 149 ± 4 | 348 ± 6 | 199 ± 5 | 101 | 145 | 74 |
| 250 | 10/10 | 148 ± 4 | 346 ± 7 | 198 ± 4 | 100 | 136 | 82 |
| 500 | 10/10 | 150 ± 4 | 328 ± 5 | 177 ± 2** | 95 | 131 | 90 |
| 1,000 | 10/10 | 150 ± 4 | 296 ± 5** | 145 ± 4** | 85 | 128 | 85 |
| Female | | | | | | | |
| 0 | 10/10 | 111 ± 2 | 206 ± 3 | 95 ± 2 | | 126 | 91 |
| 50 | 10/10 | 110 ± 2 | 203 ± 4 | 93 ± 3 | 99 | 128 | 89 |
| 100 | 10/10 | 110 ± 2 | 202 ± 2 | 92 ± 2 | 98 | 127 | 93 |
| 250 | 10/10 | 111 ± 2 | 205 ± 4 | 95 ± 4 | 100 | 126 | 91 |
| 500 | 10/10 | 108 ± 2 | 193 ± 1** | 85 ± 2* | 94 | 123 | 98 |
| 1,000 | 8/10 ^d | 110 ± 2 | 187 ± 3** | 78 ± 3** | 91 | 85 | 89 |

* Significantly different (P 0.05) from the control group by Williams' test

** P 0.01

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.

^c Water consumption is expressed as grams of water consumed per kg body weight per day.

^d Week of death: 1

due to decreased blood volume and hemoconcentration (Jain, 1986). On day 20, the erythrocytosis was replaced by a developing normocytic, normochromic, nonresponsive anemia, demonstrated by decreased hematocrit values, hemoglobin concentrations, and erythrocyte counts relative to controls in males and females exposed to 250 ppm or greater. Normocytosis, normochromia, and lack of an erythropoietic response were evidenced by the absence of changes relative to controls in mean cell volumes, mean cell hemoglobin concentrations, and reticulocyte counts, respectively. At week 13, evidence of the anemia persisted in 500 and 1,000 ppm males and expanded to all exposed females.

Albumin and total protein concentrations were increased relative to controls at various time points in males and females exposed to 100 ppm or greater. Increased albumin concentration would be consistent with dehydration and hemoconcentration; overproduction of albumin is not known to occur in any animal (Kaneko, 1989). The increase of total protein is probably a reflection of the increase of albumin. This evidence of dehydration could suggest that the severity of the anemia was tempered by the hemoconcentration and that the anemia may have been more severe than what the data indicate.

There was evidence of hepatocellular injury and/or altered hepatic function demonstrated by increased serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations that predominantly occurred in 500 and 1,000 ppm males and females relative to controls. Increases of bile acid concentrations also can indicate cholestasis. But activity of serum alkaline phosphatase, another biomarker of cholestasis, was decreased relative to controls in all exposed males and females at various time points; this suggests cholestasis was not involved. However, decreased alkaline phosphatase activity was not exposure concentration-related and, thus, could indicate chemical inhibition of the enzyme or interference with the assay method. Additionally, circulating alkaline phosphatase in a normal rat is primarily of intestinal and bone origin (Righetti and Kaplan, 1971), and fasting or food restriction causes decreases in serum alkaline phosphatase activity (Jenkins and Robinson, 1975). If rats decreased their food intake due to treatment-related toxicity or poor food palatabil-

ity, decreases in alkaline phosphatase activity relative to controls might be related to loss of the normally circulating intestinal fraction. Thus, increases in alkaline phosphatase activity due to cholestasis could be counterbalanced by the negative effect of decreased food intake. Final mean body weights of 500 and 1,000 ppm males and females were significantly less than those of the controls, supporting the possibility of decreased food intake. Changes in other hematology and clinical chemistry variables were minimal, inconsistent between males and females, and within physiological values and thus were not considered toxicologically relevant.

Epididymis and testis weights of 1,000 ppm males were significantly less than controls but were probably related to decreased body weights (Table I1). The estrous cycle length of 1,000 ppm females was significantly longer than that of the controls (Table I2).

Absolute and relative liver weights of males exposed to 250, 500, or 1,000 ppm and of females exposed to 100, 250, 500, or 1,000 ppm were significantly greater than controls (Table H1). At the end of the study, plasma concentrations of pyridine in 50, 100, 250, and 500 ppm females were greater than those in males; however, plasma concentration in 1,000 ppm females was less than in males (Table J1).

Multiple hepatic alterations were observed in the livers of males and females exposed to 500 or 1,000 ppm (Table 3). Incidences of centrilobular degeneration and hypertrophy were increased relative to controls in males and females exposed to 500 or 1,000 ppm. Incidences of chronic inflammation were increased in 1,000 ppm males and females and 500 ppm males compared to controls. Incidences of pigmentation were significantly increased in 500 and 1,000 ppm males and females and 250 ppm females relative to controls. Degeneration consisted of clusters of hepatocytes, primarily centrilobular, that were strikingly ballooned and whose rarefied cytoplasm had strands or granules of eosinophilic material. Hypertrophy was a minimal increase in the size of centrilobular hepatocytes. Chronic inflammation consisted of lymphocytes, macrophages, and fibrous connective tissue that was primarily centrilobular but bridged across lobules in more severe cases. The macrophages often contained a yellow-brown pigment that special stains showed had characteristics

of both lipofuscin and hemosiderin. The pigment was positive with PAS, Perl's, and Schmorl's staining but was acid-fast negative.

In the kidney, the incidences of granular casts and hyaline degeneration (hyaline droplets) of minimal severity were significantly increased in 1,000 ppm males and slightly increased in 500 ppm males (Table 3). Lumens from one to three tubules per kidney were filled with a granular eosinophilic material (granular casts) thought to represent cellular debris from dead and sloughed renal tubule epithelial cells from a more proximal region of the tubule.

Hyaline droplets were characterized by eosinophilic proteinaceous material within the cytoplasm of renal tubular epithelial cells. This change occurred in all kidneys from males in the 13-week study but was only diagnosed when the quantity exceeded that observed in control males. An immunohistochemical stain specific for α 2u-globulin was positive in both control and exposed males; the intensity of staining appeared slightly greater in the 1,000 ppm group. These changes, consistent with α 2u-globulin nephropathy, were minimal in 1,000 ppm males. There was marginal evidence of an effect in the 500 ppm group and a no-effect level in the 250 ppm group.

TABLE 3
Incidences of Selected Nonneoplastic Lesions in F344/N Rats in the 13-Week Drinking Water Study of Pyridine

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|----------|----------|----------|-----------|------------------------|------------|
| Male | | | | | | |
| Liver ^a | 10 | 10 | 10 | 10 | 10 | 10 |
| Centrilobular, Degeneration ^b | 0 | 0 | 0 | 0 | 9** (1.0) ^c | 9** (1.8) |
| Hypertrophy | 0 | 0 | 0 | 0 | 9** (1.0) | 9** (1.0) |
| Inflammation, Chronic | 1 (1.0) | 1 (1.0) | 1 (1.0) | 1 (1.0) | 7** (1.0) | 9** (1.9) |
| Pigmentation | 0 | 0 | 0 | 0 | 6** (1.0) | 10** (1.1) |
| Kidney | 10 | 10 | 10 | 10 | 10 | 10 |
| Casts | 0 | 0 | 3 (1.0) | 3 (1.0) | 9** (1.0) | 9** (1.0) |
| Inflammation, Chronic | 0 | 0 | 0 | 2 (1.0) | 4* (1.0) | 9** (1.0) |
| Mineralization | 2 (1.0) | 2 (1.0) | 2 (1.0) | 6 (1.0) | 9** (1.0) | 10** (1.0) |
| Renal Tubule, Regeneration | 10 (1.0) | 10 (1.0) | 10 (1.0) | 10 (1.1) | 10 (1.6) | 10 (1.4) |
| Casts Granular | 0 | 0 | 0 | 0 | 3 (1.0) | 8** (1.0) |
| Renal Tubule, Hyaline Degeneration | 1 (1.0) | 0 | 1 (1.0) | 1 (1.0) | 3 (1.0) | 7** (1.0) |
| Female | | | | | | |
| Liver | 10 | 10 | 10 | 10 | 10 | 10 |
| Centrilobular, Degeneration | 0 | 0 | 0 | 0 | 9** (1.0) | 9** (1.8) |
| Hypertrophy | 0 | 0 | 0 | 0 | 9** (1.0) | 8** (1.0) |
| Inflammation, Chronic | 0 | 0 | 0 | 0 | 1 (1.0) | 4* (1.8) |
| Pigmentation | 0 | 0 | 0 | 7** (1.0) | 7** (1.0) | 8** (1.1) |
| Kidney | 10 | | | | | 10 |
| Casts | 0 | | | | | 2 (1.0) |
| Mineralization | 10 (1.6) | | | | | 10 (1.3) |

* Significantly different (P 0.05) from the control group by the Fisher exact test

** P 0.01

^a Number examined microscopically

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Additionally, there were increased incidences and/or severities of protein casts, chronic inflammation, mineralization, and regeneration primarily in 500 and 1,000 ppm males. These lesions are qualitatively similar to those associated with spontaneous nephropathy observed in young control male F344/N rats and may have been exacerbated by administration of pyridine. Exacerbation of these lesions also occurs with α 2u-globulin nephropathy and may have contributed to the increases observed in this study.

Exposure Concentration Selection Rationale: The highest exposure concentration selected for the 2-year F344/N rat study was 400 ppm based on increased incidences and severities of liver (including increased

alanine aminotransferase and sorbitol dehydrogenase activities and bile acids concentrations) and kidney lesions and lower final mean body weights and body weight gains relative to controls in rats exposed to 500 or 1,000 ppm in the 13-week study. Lesions observed in the liver of female rats exposed to 250 ppm consisted of only scant pigment in macrophages in the vicinity of the central veins, and there was no effect on the kidney. Pyridine plasma levels were measured at the end of the 13-week studies in rats (Tables J1 and J2). A clear inflection point in the serum levels cannot be determined from the pyridine data, but the serum levels at 500 and 1,000 ppm appear disproportionately high when compared to those at 100 and 250 ppm.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female F344/N rats are shown in Table 4 and in the Kaplan-Meier survival curves (Figure 2). Survival of exposed males and females was not significantly different from controls.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of 400 ppm males and females were generally less than those of controls throughout

the study, and those of 200 ppm males and females were generally less during the second year of the study (Figure 3; Tables 5 and 6). Water consumption by 400 ppm males and females was greater than that by controls throughout the study, and water consumption by 200 ppm males and females was greater during the second year of the study (Tables L1 and L2). Drinking water concentrations of 100, 200, or 400 ppm pyridine resulted in average daily doses of 7, 14, or 33 mg/kg. There were no treatment-related clinical findings.

TABLE 4
Survival of F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|---------|----------|---------|---------|
| Male | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Moribund | 11 | 13 | 15 | 10 |
| Natural deaths | 14 | 17 | 10 | 24 |
| Animals surviving to study termination | 25 | 20 | 25 | 16 |
| Percent probability of survival at end of study ^a | 50 | 40 | 50 | 32 |
| Mean survival (days) ^b | 663 | 666 | 665 | 646 |
| Survival analysis ^c | P=0.124 | P=0.403 | P=1.000 | P=0.095 |
| Female | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Moribund | 3 | 8 | 7 | 2 |
| Natural deaths | 15 | 5 | 14 | 22 |
| Animals surviving to study termination | 32 | 37 | 29 | 26 |
| Percent probability of survival at end of study | 64 | 74 | 58 | 52 |
| Mean survival (days) | 694 | 703 | 693 | 672 |
| Survival analysis | P=0.055 | P=0.392N | P=0.700 | P=0.204 |

^a Kaplan-Meier determinations

^b Mean of all deaths (uncensored, censored, and terminal sacrifice)

^c The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. Lower mortality in an exposure group is indicated by N.

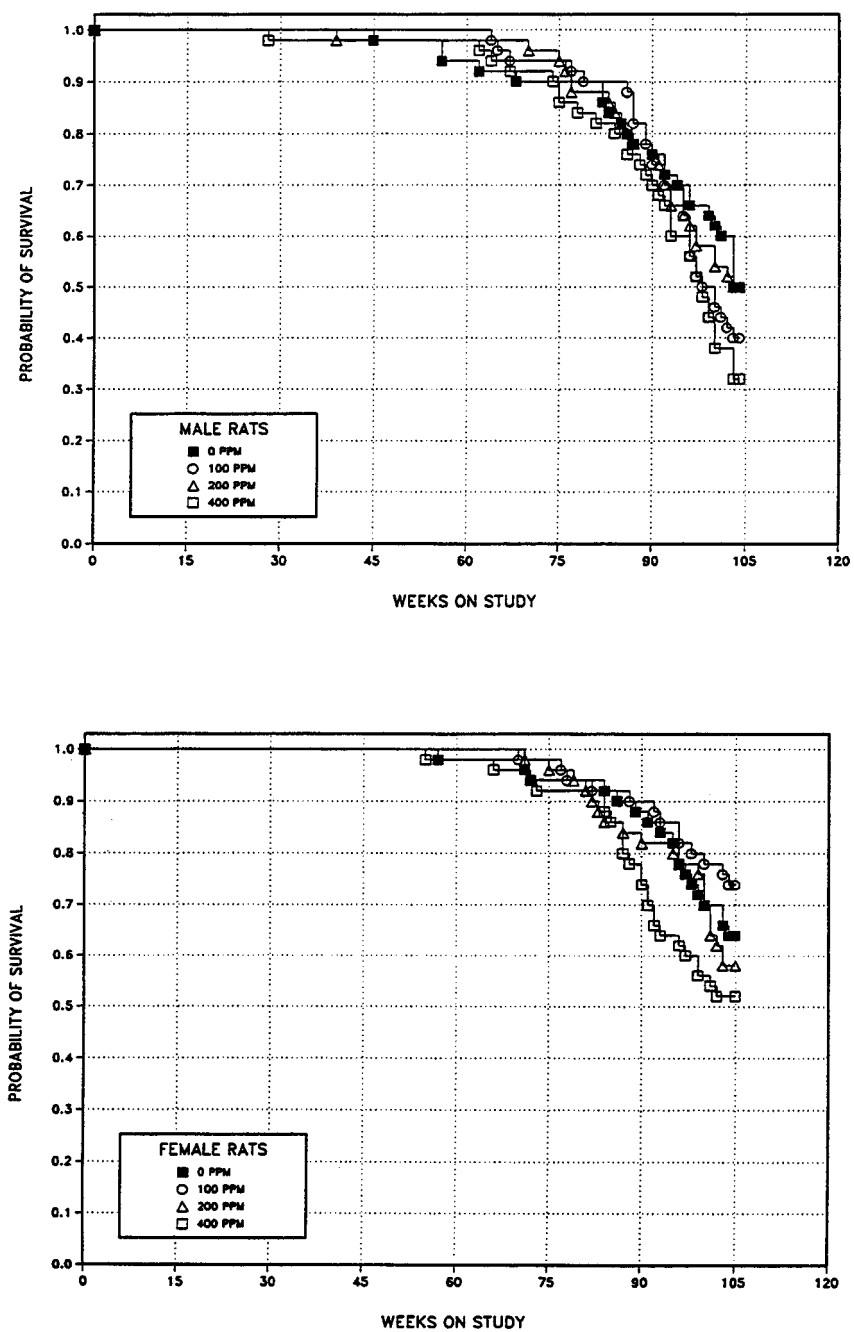


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female F344/N Rats
Exposed to Pyridine in Drinking Water for 2 Years

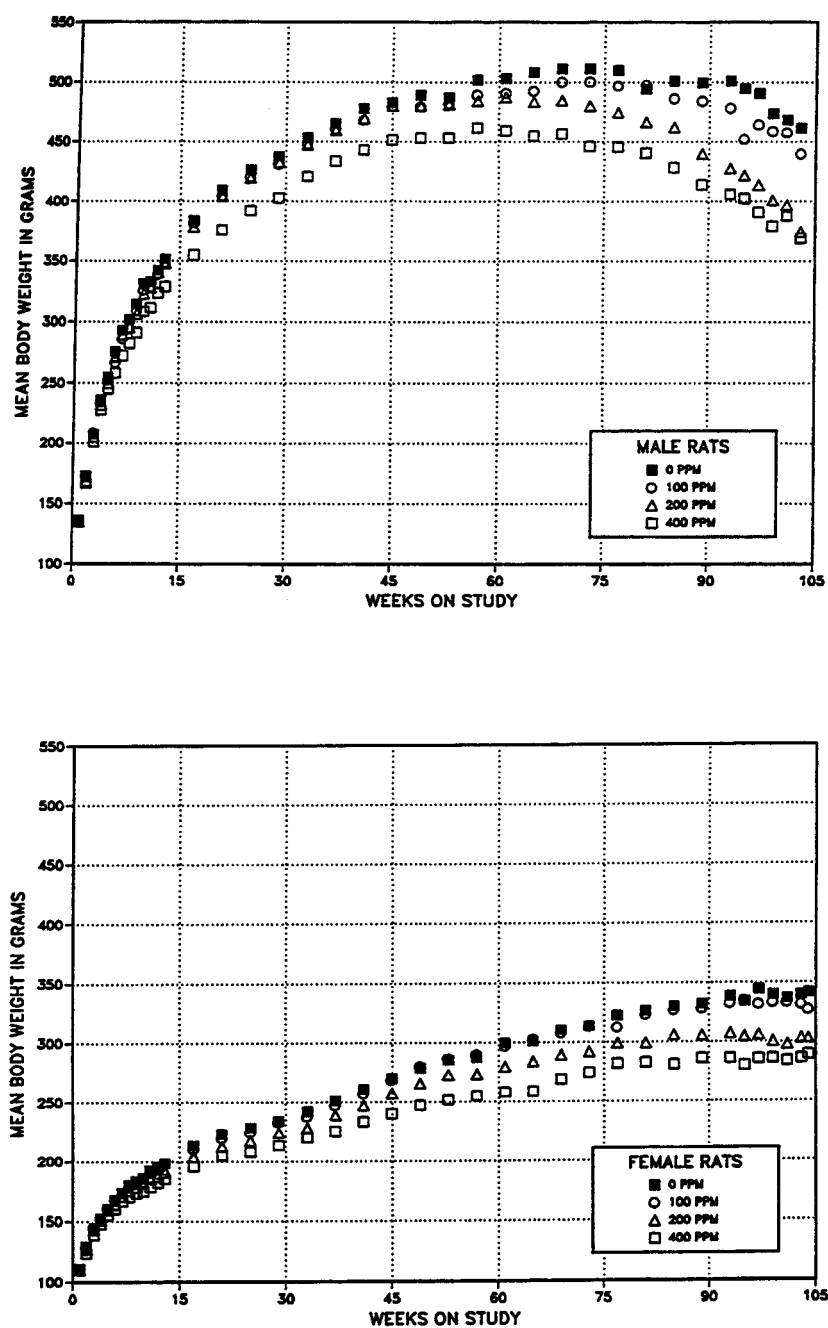


FIGURE 3
Growth Curves for Male and Female F344/N Rats
Exposed to Pyridine in Drinking Water for 2 Years

TABLE 5
Mean Body Weights and Survival of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| Weeks on Study | 0 ppm | | 100 ppm | | | 200 ppm | | | 400 ppm | | |
|-----------------------|----------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 136 | 50 | 135 | 99 | 50 | 135 | 99 | 50 | 136 | 100 | 50 |
| 2 | 173 | 50 | 172 | 100 | 50 | 169 | 98 | 50 | 167 | 97 | 50 |
| 3 | 207 | 50 | 208 | 101 | 50 | 206 | 99 | 50 | 201 | 97 | 50 |
| 4 | 236 | 50 | 234 | 99 | 50 | 232 | 98 | 50 | 227 | 96 | 50 |
| 5 | 255 | 50 | 253 | 99 | 50 | 250 | 98 | 50 | 245 | 96 | 50 |
| 6 | 275 | 50 | 267 | 97 | 50 | 272 | 99 | 50 | 258 | 94 | 50 |
| 7 | 293 | 50 | 286 | 98 | 50 | 289 | 99 | 50 | 272 | 93 | 50 |
| 8 | 302 | 50 | 295 | 98 | 50 | 295 | 98 | 50 | 282 | 94 | 50 |
| 9 | 314 | 50 | 309 | 98 | 50 | 306 | 97 | 50 | 291 | 93 | 50 |
| 10 | 331 | 50 | 326 | 99 | 50 | 323 | 98 | 50 | 309 | 93 | 50 |
| 11 | 333 | 50 | 329 | 99 | 50 | 328 | 99 | 50 | 311 | 94 | 50 |
| 12 | 342 | 50 | 339 | 99 | 50 | 340 | 100 | 50 | 323 | 95 | 50 |
| 13 | 351 | 50 | 349 | 99 | 50 | 348 | 99 | 50 | 328 | 94 | 50 |
| 17 | 384 | 50 | 382 | 100 | 50 | 378 | 99 | 50 | 355 | 93 | 50 |
| 21 | 409 | 50 | 405 | 99 | 50 | 404 | 99 | 50 | 376 | 92 | 50 |
| 25 | 426 | 50 | 420 | 99 | 50 | 420 | 98 | 50 | 392 | 92 | 50 |
| 29 | 437 | 50 | 431 | 99 | 50 | 433 | 99 | 50 | 403 | 92 | 49 |
| 33 | 453 | 50 | 448 | 99 | 50 | 448 | 99 | 50 | 421 | 93 | 49 |
| 37 | 465 | 50 | 461 | 99 | 50 | 460 | 99 | 50 | 434 | 93 | 49 |
| 41 | 478 | 50 | 468 | 98 | 50 | 469 | 98 | 49 | 443 | 93 | 49 |
| 45 | 483 | 50 | 480 | 99 | 50 | 480 | 100 | 49 | 452 | 94 | 49 |
| 49 | 489 | 49 | 479 | 98 | 50 | 480 | 98 | 49 | 453 | 93 | 49 |
| 53 | 487 | 49 | 482 | 99 | 50 | 482 | 99 | 49 | 453 | 93 | 49 |
| 57 | 502 | 47 | 489 | 98 | 50 | 484 | 97 | 49 | 462 | 92 | 49 |
| 61 | 503 | 47 | 491 | 98 | 50 | 487 | 97 | 49 | 459 | 91 | 49 |
| 65 | 508 | 46 | 492 | 97 | 49 | 484 | 95 | 49 | 455 | 90 | 47 |
| 69 | 511 | 45 | 500 | 98 | 47 | 485 | 95 | 49 | 457 | 89 | 46 |
| 73 | 511 | 45 | 500 | 98 | 47 | 480 | 94 | 48 | 446 | 87 | 46 |
| 77 | 510 | 45 | 497 | 98 | 47 | 475 | 93 | 46 | 446 | 87 | 43 |
| 81 | 494 | 45 | 497 | 101 | 45 | 467 | 94 | 44 | 441 | 89 | 42 |
| 85 | 501 | 42 | 486 | 97 | 45 | 462 | 92 | 41 | 428 | 86 | 40 |
| 89 | 499 | 39 | 484 | 97 | 41 | 440 | 88 | 39 | 414 | 83 | 37 |
| 93 | 501 | 36 | 478 | 95 | 35 | 428 | 85 | 35 | 406 | 81 | 33 |
| 95 | 495 | 35 | 452 | 91 | 35 | 422 | 85 | 33 | 403 | 81 | 30 |
| 97 | 491 | 33 | 464 | 95 | 28 | 414 | 84 | 30 | 391 | 80 | 28 |
| 99 | 474 | 33 | 459 | 97 | 25 | 401 | 85 | 29 | 379 | 80 | 24 |
| 101 | 468 | 31 | 458 | 98 | 23 | 397 | 85 | 27 | 388 | 83 | 19 |
| 103 | 461 | 29 | 440 | 95 | 21 | 374 | 81 | 26 | 369 | 80 | 19 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 273 | | 269 | 99 | | 269 | 99 | | 258 | 95 | |
| 14-52 | 447 | | 442 | 99 | | 441 | 99 | | 414 | 93 | |
| 53-103 | 495 | | 479 | 97 | | 449 | 91 | | 425 | 86 | |

TABLE 6
Mean Body Weights and Survival of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| Weeks on Study | 0 ppm | | 100 ppm | | | 200 ppm | | | 400 ppm | | |
|-----------------------|----------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 110 | 50 | 110 | 100 | 50 | 110 | 101 | 50 | 111 | 101 | 50 |
| 2 | 129 | 50 | 128 | 99 | 50 | 127 | 99 | 50 | 124 | 96 | 50 |
| 3 | 144 | 50 | 145 | 100 | 50 | 143 | 99 | 50 | 139 | 96 | 50 |
| 4 | 152 | 50 | 152 | 100 | 50 | 151 | 99 | 50 | 148 | 97 | 50 |
| 5 | 160 | 50 | 160 | 100 | 50 | 159 | 100 | 50 | 155 | 97 | 50 |
| 6 | 167 | 50 | 167 | 100 | 50 | 164 | 98 | 50 | 160 | 96 | 50 |
| 7 | 173 | 50 | 173 | 100 | 50 | 171 | 98 | 50 | 167 | 96 | 50 |
| 8 | 180 | 50 | 179 | 100 | 50 | 176 | 98 | 50 | 170 | 95 | 50 |
| 9 | 183 | 50 | 183 | 100 | 50 | 178 | 97 | 50 | 173 | 94 | 50 |
| 10 | 186 | 50 | 185 | 100 | 50 | 181 | 98 | 50 | 175 | 94 | 50 |
| 11 | 192 | 50 | 190 | 99 | 50 | 185 | 96 | 50 | 178 | 93 | 50 |
| 12 | 196 | 50 | 194 | 99 | 50 | 187 | 96 | 50 | 182 | 93 | 50 |
| 13 | 198 | 50 | 197 | 100 | 50 | 191 | 97 | 50 | 185 | 93 | 50 |
| 17 | 213 | 50 | 210 | 99 | 50 | 204 | 96 | 50 | 196 | 92 | 50 |
| 21 | 223 | 50 | 220 | 99 | 50 | 212 | 95 | 50 | 205 | 92 | 50 |
| 25 | 228 | 50 | 225 | 99 | 50 | 218 | 95 | 50 | 208 | 91 | 50 |
| 29 | 234 | 50 | 233 | 100 | 50 | 224 | 96 | 50 | 214 | 91 | 50 |
| 33 | 242 | 50 | 238 | 98 | 50 | 228 | 94 | 50 | 220 | 91 | 50 |
| 37 | 251 | 50 | 247 | 98 | 50 | 239 | 95 | 50 | 225 | 90 | 50 |
| 41 | 261 | 50 | 257 | 99 | 50 | 247 | 95 | 50 | 234 | 90 | 50 |
| 45 | 270 | 50 | 269 | 100 | 50 | 257 | 95 | 50 | 240 | 89 | 50 |
| 49 | 279 | 50 | 280 | 101 | 50 | 266 | 95 | 50 | 247 | 89 | 50 |
| 53 | 285 | 50 | 287 | 101 | 50 | 273 | 96 | 50 | 252 | 88 | 50 |
| 57 | 288 | 50 | 290 | 101 | 50 | 273 | 95 | 50 | 255 | 89 | 49 |
| 61 | 299 | 49 | 297 | 99 | 50 | 280 | 94 | 50 | 258 | 86 | 49 |
| 65 | 301 | 49 | 302 | 100 | 50 | 284 | 94 | 50 | 259 | 86 | 49 |
| 69 | 310 | 49 | 308 | 99 | 50 | 290 | 93 | 50 | 269 | 87 | 48 |
| 73 | 314 | 47 | 313 | 100 | 49 | 292 | 93 | 49 | 275 | 88 | 47 |
| 77 | 322 | 47 | 313 | 97 | 49 | 299 | 93 | 48 | 282 | 88 | 46 |
| 81 | 326 | 47 | 323 | 99 | 47 | 299 | 92 | 47 | 283 | 87 | 46 |
| 85 | 330 | 46 | 327 | 99 | 46 | 306 | 93 | 43 | 281 | 85 | 44 |
| 89 | 331 | 45 | 328 | 99 | 45 | 306 | 92 | 42 | 286 | 86 | 39 |
| 93 | 338 | 43 | 332 | 98 | 44 | 307 | 91 | 41 | 286 | 85 | 33 |
| 95 | 334 | 42 | 335 | 100 | 43 | 305 | 91 | 41 | 281 | 84 | 32 |
| 97 | 344 | 38 | 332 | 96 | 41 | 306 | 89 | 39 | 286 | 83 | 30 |
| 99 | 340 | 36 | 333 | 98 | 40 | 301 | 89 | 38 | 286 | 84 | 29 |
| 101 | 337 | 35 | 333 | 99 | 39 | 298 | 89 | 35 | 284 | 85 | 28 |
| 103 | 340 | 35 | 332 | 98 | 39 | 303 | 89 | 31 | 286 | 84 | 26 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 167 | | 166 | 99 | | 163 | 98 | | 159 | 95 | |
| 14-52 | 245 | | 242 | 99 | | 233 | 95 | | 221 | 90 | |
| 53-103 | 321 | | 318 | 99 | | 295 | 92 | | 276 | 86 | |

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the kidney, liver, and lung and incidences of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male F344/N rats and Appendix B for female F344/N rats.

Kidney: In the standard evaluation, the number of renal tubule adenomas in male rats exposed to 400 ppm was significantly greater than in the controls and exceeded the historical control range (Tables 7, A3, and A4). One renal tubule carcinoma was observed in a 100 ppm male. Additional step sections of kidneys were prepared from residual wet tissue so that each kidney yielded four additional sections spaced 1 mm apart. The step sections did not reveal additional carcinomas,

but additional adenomas were observed in each group of exposed and control males (Table 7). The incidence of renal tubule hyperplasia was increased in 400 ppm males in single sections compared to controls (Tables 7 and A5).

Renal tubule hyperplasia consisted of multiple layers rather than the normal single layer of epithelium, frequently resulting in an increased tubule diameter (Plate 1). Severity of hyperplasia depended on the number of layers and the complexity of their patterns. Some had papillary projections, but cells retained their orientation to the basement membrane. The renal tubule adenomas in both single and step sections were typical of those occurring spontaneously. Adenomas were masses of epithelial cells five or more tubule diameters in size (Plate 2). Cells in the adenomas were disorganized and had lost their orientation to the tubule basement membrane. The renal tubule carcinoma observed in the single sections was approximately 3 mm in diameter and had densely packed, widely pleomorphic epithelial cells that infiltrated the adjacent parenchyma.

TABLE 7
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Male F344/N Rats
in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|-----------------------|----------------|-----------|------------|
| Kidney | 50 | 48 | 50 | 49 |
| Single Sections (Standard Evaluation) | | | | |
| Nephropathy ^a | 47 (2.3) ^b | 47 (2.3) | 49 (2.5) | 49 (2.6) |
| Renal Tubule, Hyperplasia | 1 (1.0) | 0 | 4 (3.0) | 7* (1.7) |
| Renal Tubule, Adenoma ^c (includes multiple) | | | | |
| Overall rate ^d | 1/50 (2%) | 0/48 (0%) | 2/50 (4%) | 6/49 (12%) |
| Adjusted rate ^e | 2.4% | 0.0% | 4.9% | 15.9% |
| Terminal rate ^f | 1/25 (4%) | 0/20 (0%) | 1/25 (4%) | 2/16 (13%) |
| First incidence (days) | 722 (T) | — ^h | 708 | 644 |
| Poly-3 test ^g | P=0.003 | P=0.510N | P=0.498 | P=0.042 |
| Renal Tubule, Carcinoma ⁱ | 0 | 1 | 0 | 0 |
| Renal Tubule, Adenoma or Carcinoma ^c | | | | |
| Overall rate | 1/50 (2%) | 1/48 (2%) | 2/50 (4%) | 6/49 (12%) |
| Adjusted rate | 2.4% | 2.6% | 4.9% | 15.9% |
| Terminal rate | 1/25 (4%) | 1/20 (5%) | 1/25 (4%) | 2/16 (13%) |
| First incidence (days) | 722 (T) | 722 (T) | 708 | 644 |
| Poly-3 test | P=0.008 | P=0.750 | P=0.498 | P=0.042 |

TABLE 7
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Male F344/N Rats
in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|-----------|------------|------------|-------------|
| Step Sections (Extended Evaluation) | | | | |
| Renal Tubule, Hyperplasia | 9 (2.0) | 7 (2.1) | 11 (3.0) | 15 (2.4) |
| Renal Tubule, Adenoma | 1 | 3 | 5 | 9** |
| Single Sections and Step Sections (Combined) | | | | |
| Renal Tubule, Hyperplasia | 10 (1.9) | 7 (2.1) | 14 (3.1) | 16 (2.4) |
| Renal Tubule, Adenoma | | | | |
| Overall rate | 2/50 (4%) | 3/48 (6%) | 6/50 (12%) | 10/49 (20%) |
| Adjusted rate | 4.9% | 7.6% | 14.5% | 26.3% |
| Terminal rate | 2/25 (8%) | 2/20 (10%) | 3/25 (12%) | 5/16 (31%) |
| First incidence (days) | 722 (T) | 673 | 627 | 644 |
| Poly-3 test | P=0.002 | P=0.480 | P=0.133 | P=0.008 |
| Renal Tubule, Carcinoma | 0 | 1 | 0 | 0 |
| Renal Tubule, Adenoma or Carcinoma | | | | |
| Overall rate | 2/50 (4%) | 4/48 (8%) | 6/50 (12%) | 10/49 (20%) |
| Adjusted rate | 4.9% | 10.2% | 14.5% | 26.3% |
| Terminal rate | 2/25 (8%) | 3/20 (15%) | 3/25 (12%) | 5/16 (31%) |
| First incidence (days) | 722 (T) | 673 | 627 | 644 |
| Poly-3 test | P=0.003 | P=0.316 | P=0.133 | P=0.008 |
| Stomach, Glandular | 50 | 49 | 50 | 49 |
| Mineralization | 0 | 2 (2.0) | 2 (1.5) | 8** (2.0) |
| Parathyroid Gland | 50 | 50 | 50 | 48 |
| Hyperplasia | 0 | 1 (2.0) | 3 (2.3) | 3 (2.0) |
| Bone | 50 | 50 | 50 | 50 |
| Fibrous Osteodystrophy | 2 (3.0) | 1 (3.0) | 4 (2.3) | 6 (2.5) |

* Significantly different (P 0.05) from the control group by the Poly-3 test

** P 0.01

(T)Terminal sacrifice

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

^c Historical incidence for 2-year drinking water studies with untreated control groups (mean ± standard deviation): 1/327 (0.3% ± 0.8%); range, 0%-2%

^d Number of animals with neoplasm per number of animals with kidney examined microscopically

^e Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^f Observed incidence at terminal kill

^g Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by N.

^h Not applicable; no neoplasms in animal group

ⁱ Historical incidence: 0/327

The severity of nephropathy was not significantly increased in males (Table 7). Incidences of mineralization of the stomach, parathyroid gland hyperplasia, and fibrous osteodystrophy were observed in a few

exposed males, and the incidence of stomach mineralization in 400 ppm males was significantly increased compared to controls (Tables 7 and A5). These extra-renal lesions are indicative of kidney disease.

Mononuclear Cell Leukemia: Incidences of mononuclear cell leukemia in female rats were significantly increased in the 200 and 400 ppm groups compared to controls, and the incidence in the 400 ppm group exceeded the historical control range (Tables 8, B3, and B4). In all animals with this neoplasm, neoplastic cells were found in the spleen and usually also in the

liver. Infiltrations in the lung, bone marrow, lymph nodes, adrenal gland, and kidney were also common. Incidences of mononuclear cell leukemia in male rats were similar to those in controls (0 ppm, 29/50; 100 ppm, 32/50; 200 ppm, 26/50; 400 ppm, 27/50; Table A3).

TABLE 8
Incidences of Mononuclear Cell Leukemia in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|-------------|-------------|-------------|-------------|
| Mononuclear Cell Leukemia ^a | | | | |
| Overall rate ^b | 12/50 (24%) | 16/50 (32%) | 22/50 (44%) | 23/50 (46%) |
| Adjusted rate ^c | 26.5% | 34.3% | 45.4% | 48.7% |
| Terminal rate ^d | 8/32 (25%) | 12/37 (32%) | 8/29 (28%) | 5/26 (19%) |
| First incidence (days) | 636 | 546 | 496 | 380 |
| Poly-3 test ^e | P=0.013 | P=0.279 | P=0.043 | P=0.020 |

^a Historical incidence for 2-year drinking water studies with untreated control groups (mean \pm standard deviation): 102/330 (30.9% \pm 10.0%); range, 16%-44%

^b Number of animals necropsied

^c Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^d Observed incidence at terminal kill

^e Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.

Liver: Incidences of hepatocellular neoplasms were not significantly increased in exposed rats compared to controls, but exposure concentration-related nonneoplastic liver lesions were observed (Tables 9, A5, and B5). Incidences of centrilobular cytomegaly and cytoplasmic vacuolization were increased in males exposed to 200 or 400 ppm and females exposed to 400 ppm relative to controls. In 400 ppm males, incidences of periportal fibrosis, fibrosis, and centrilobular degeneration and necrosis were significantly increased relative to controls. The incidence of centrilobular degeneration was increased in 400 ppm females compared to controls. Bile duct hyperplasia was observed in control and exposed males and females, and the incidences were significantly increased in exposed females compared to controls. Incidences of pigmentation increased compared to controls in all exposed groups of males and in 400 ppm females. Incidences of basophilic foci were decreased relative to controls in

200 and 400 ppm males and all exposed groups of females. The incidence of clear cell foci relative to controls was decreased in 100 ppm males; incidences of clear cell foci were increased relative to controls in 200 and 400 ppm females. The incidence of eosinophilic foci was increased relative to controls in 100 ppm males.

Centrilobular cytomegaly consisted of an increased amount of cytoplasm containing varying amounts of homogeneous eosinophilic material that enlarged hepatocytes. Cytoplasmic vacuolization referred to vacuolized hepatocytes in noncentrilobular areas. Periportal fibrosis consisted of bands of fibrous connective tissue in portal areas. Fibrosis was defined as fibrous connective tissue under the capsule of the liver and extending downward along the vasculature. Bile duct hyperplasia was a cluster of six or more bile ducts. Pigmentation was yellowish brown material in

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in F344/N Rats
in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|-------------------------------------|----------|----------------------|------------|------------|
| Male | | | | |
| Number Examined Microscopically | 50 | 49 | 50 | 50 |
| Basophilic Focus ^a | 12 | 5 | 0** | 1** |
| Clear Cell Focus | 7 | 1* | 7 | 4 |
| Eosinophilic Focus | 14 | 23* | 23 | 13 |
| Centrilobular, Cytomegaly | 0 | 4 (1.3) ^b | 8** (1.3) | 6* (2.0) |
| Vacuolization Cytoplasmic | 4 (1.5) | 6 (1.8) | 13* (1.7) | 17** (2.4) |
| Periportal Fibrosis | 0 | 0 | 2 (2.5) | 29** (1.8) |
| Fibrosis | 1 (2.0) | 1 (2.0) | 1 (1.0) | 10** (1.6) |
| Centrilobular, Degeneration | 1 (2.0) | 3 (2.3) | 2 (2.0) | 8* (2.1) |
| Centrilobular, Necrosis | 0 | 3 (1.7) | 0 | 5* (2.2) |
| Bile Duct, Hyperplasia | 46 (1.4) | 43 (1.5) | 44 (1.6) | 49 (1.6) |
| Pigmentation | 4 (1.0) | 11* (1.3) | 20** (1.3) | 25** (2.0) |
| Hepatocellular Adenoma | 1 | 1 | 0 | 3 |
| Hepatocellular Carcinoma | 0 | 0 | 1 | 0 |
| Hepatocellular Adenoma or Carcinoma | 1 | 1 | 1 | 3 |
| Female | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Basophilic Focus | 38 | 28* | 11** | 0** |
| Clear Cell Focus | 4 | 9 | 11* | 16** |
| Eosinophilic Focus | 19 | 24 | 22 | 15 |
| Centrilobular, Cytomegaly | 0 | 1 (1.0) | 4 (1.0) | 20** (1.4) |
| Vacuolization Cytoplasmic | 10 (1.8) | 7 (1.0) | 9 (1.8) | 18* (1.6) |
| Centrilobular, Degeneration | 1 (2.0) | 2 (2.5) | 2 (1.5) | 7* (1.1) |
| Bile Duct, Hyperplasia | 20 (1.0) | 29* (1.1) | 34** (1.0) | 29* (1.0) |
| Pigmentation | 6 (1.5) | 2 (1.5) | 6 (2.3) | 17** (1.6) |
| Hepatocellular Adenoma | 1 | 0 | 1 | 0 |

* Significantly different (P 0.05) from the control group by the Poly-3 test

** P 0.01

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

macrophages, often present in areas of fibrosis. Centrilobular degeneration was used to denote vacuolated hepatocytes in the center of hepatic lobules.

Lung: Incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in males occurred with a positive trend (1/50, 0/50, 2/50, 4/50; Table A3). Alveolar

epithelial hyperplasia was also observed in the 100 and 400 ppm groups (0/50, 3/50, 0/50, 3/50; Table A5). Although these neoplasms are relatively uncommon, incidences up to eight of 50 have occurred in untreated control groups from other recent NTP 2-year carcinogenicity studies. This marginally increased neoplasm incidence was not considered to be chemical-related.

WISTAR RATS

13-WEEK STUDY

One male rat exposed to 500 ppm died during the first week of the study (Table 10). Final mean body weights and body weight gains of rats exposed to 250, 500, or 1,000 ppm were significantly less than those of the controls. Water consumption by rats exposed to

1,000 ppm was lower than that by controls. Drinking water concentrations of 50, 100, 250, 500, or 1,000 ppm pyridine resulted in average daily doses of 5, 10, 30, 60, or 100 mg/kg. There were no treatment-related clinical findings.

TABLE 10
Survival, Body Weights, and Water Consumption of Male Wistar Rats
in the 13-Week Drinking Water Study of Pyridine

| Concentration (ppm) | Survival ^a | Mean Body Weight ^b (g) | | | Final Weight Relative to Controls (%) | Water Consumption ^c | |
|------------------------|-----------------------|-----------------------------------|------------|------------|--|-----------------------------------|---------|
| | | Initial | Final | Change | | Week 1 | Week 13 |
| 0 | 10/10 | 161 ± 3 | 511 ± 9 | 350 ± 9 | | 169 | 120 |
| 50 | 10/10 | 161 ± 3 | 476 ± 13 | 315 ± 11 | 93 | 152 | 118 |
| 100 | 10/10 | 159 ± 3 | 490 ± 7 | 331 ± 8 | 96 | 148 | 116 |
| 250 | 10/10 | 159 ± 3 | 463 ± 17** | 304 ± 16** | 91 | 136 | 95 |
| 500 | 9/10 ^d | 157 ± 4 | 443 ± 8** | 286 ± 6** | 87 | 141 | 127 |
| 1,000 | 10/10 | 159 ± 3 | 420 ± 15** | 260 ± 14** | 82 | 111 | 74 |

** Significantly different (P 0.01) from the control group by Williams' test

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.

^c Water consumption is expressed as grams of water consumed per kg body weight per day.

^d Week of death: 1

The hematology and clinical chemistry data for Wistar rats are presented in Table G2. Similar to male F344/N rats, an erythrocytosis, demonstrated by increased hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred in 500 and 1,000 ppm rats on day 5. An erythrocytosis would be consistent with dehydration, which can cause a relative erythrocytosis due to decreased blood volume and hemoconcentration. Hemoconcentration would be supported by the increased albumin concentration in 1,000 ppm rats relative to controls. Additionally, urea nitrogen concentrations were increased relative to controls in 500 and 1,000 ppm rats on days 5 and 20; creatinine concentration, another marker of renal function, was unaffected. Urea nitrogen concentration can be influenced by many extrarenal factors: high protein diets, dehydration, liver function, animal health, and nutritional status (Finco, 1989). Serum creatinine, a product of muscle metabolism, is not as affected by extrarenal

factors (Ragan, 1989). A nonrenal effect, such as dehydration caused by decreased water intake due to poor palatability of dosed water, could result in a urea nitrogen concentration increase, while creatinine concentration remains unchanged.

Also similar to F344/N rats, there was evidence of hepatocellular injury and/or altered hepatic function demonstrated by increased serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations at all time points in 500 and 1,000 ppm rats relative to controls. Decreased alkaline phosphatase activity relative to controls was observed, but with less consistency, in 250 and 1,000 ppm rats.

Organ weights of exposed rats were not significantly different from those of controls (Table H2). Plasma concentrations of pyridine increased with increasing dose (Table J2).

Incidences of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation in the liver of rats exposed to 500 or 1,000 ppm were significantly increased relative to controls (Table 11). Two types of enlarged centrilobular hepatocytes were separately diagnosed. Degeneration consisted of mildly to moderately enlarged, palely stained hepatocytes, primarily centrilobular, that had lacy to vacuolated cytoplasm containing an eosinophilic granular to flocculent material. Hypertrophy was a minimal increase in size of centrilobular hepatocytes without vacuolated or lacy cytoplasm. Chronic inflammation consisted of lymphocytes, macrophages, and fibrous connective tissue that was primarily centrilobular and bridged across lobules in more severe cases. The macrophages often contained a yellow-brown pigment that special stains showed had characteristics of both lipofuscin and hemosiderin. The pigment was positive with PAS, Perl's, and Schmorl's staining but was acid-fast negative.

Incidences of kidney lesions in exposed rats were not significantly different from those of controls (Table 11). Many lesions (protein casts, inflammation mineralization, and regeneration of renal tubule epithelium) are components of spontaneous nephropathy

that is common in male rats. The incidences of spontaneous nephropathy in control Wistar males were high, and possible nephrotoxicity was not clear. Granular casts, which indicate more severe renal tubule damage than protein casts, were noted in one rat in the 1,000 ppm group. The incidence, but not the severity, of hyaline degeneration was increased, although not significantly, in the 1,000 ppm group. Hyaline degeneration refers to eosinophilic refractile protein material in the cytoplasm of renal tubule epithelium. Immunohistochemistry for α 2u-globulin was positive in all males tested.

Exposure Concentration Selection Rationale: The highest exposure concentration selected for the 2-year Wistar rat study was 400 ppm based on increased incidences and severities of liver lesions (including increased alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations) in rats exposed to 500 or 1,000 ppm compared to controls. Pyridine plasma levels were measured at the end of the 13-week studies in rats (Tables J1 and J2). A clear inflection point in the serum levels could not be determined from the pyridine data, but the serum levels at 500 and 1,000 ppm appeared disproportionately high when compared to those at 100 and 250 ppm.

TABLE 11
Incidences of Selected Nonneoplastic Lesions in Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|---------|---------|---------|---------|------------------------|------------|
| Liver ^a | 10 | 10 | 10 | 10 | 9 | 10 |
| Centrilobular, Degeneration ^b | 0 | 0 | 0 | 0 | 9** (1.7) ^c | 9** (1.4) |
| Hypertrophy | 0 | 0 | 0 | 0 | 9** (1.0) | 10** (1.0) |
| Inflammation, Chronic | 0 | 0 | 0 | 2 (1.0) | 9** (1.7) | 9** (2.2) |
| Pigmentation | 0 | 0 | 0 | 0 | 9** (1.0) | 9** (1.3) |
| Kidney | 10 | 10 | 10 | 10 | 9 | 10 |
| Casts | 3 (1.0) | 3 (1.0) | 4 (1.0) | 4 (1.5) | 4 (1.0) | 5 (1.0) |
| Inflammation, Chronic | 0 | 1 (1.0) | 1 (2.0) | 0 | 0 | 2 (1.0) |
| Mineralization | 7 (1.0) | 5 (1.2) | 4 (1.0) | 8 (1.3) | 8 (1.0) | 10 (1.0) |
| Renal Tubule, Regeneration | 5 (1.0) | 6 (1.0) | 5 (1.0) | 9 (1.0) | 7 (1.0) | 8 (1.1) |
| Casts Granular | 0 | 0 | 0 | 0 | 0 | 1 (1.0) |
| Renal Tubule, Hyaline Degeneration | 2 (1.0) | 0 | 0 | 2 (1.0) | 3 (1.0) | 6 (1.0) |

** Significantly different (P 0.01) from the control group by the Fisher exact test

^a Number examined microscopically

^b Number of animals with lesion

^c Average severity grade of lesion in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male Wistar rats are shown in Table 12 and in the Kaplan-Meier survival curves (Figure 4). Survival of rats exposed to 200 or 400 ppm was significantly less than that of the controls.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of rats exposed to 100, 200, or 400 ppm were significantly less than controls (Figure 5 and Table 13). Water consumption by exposed rats was similar to that by controls (Table L3). Drinking water concentrations of 100, 200, or 400 ppm pyridine resulted in average daily doses of 8, 17, or 36 mg/kg. There were no treatment-related clinical findings.

TABLE 12

Survival of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|---------|---------|---------|---------|
| Animals initially in study | 50 | 50 | 50 | 50 |
| Moribund | 2 | 9 | 9 | 10 |
| Natural deaths | 26 | 27 | 30 | 33 |
| Animals surviving to study termination | 22 | 14 | 11 | 7 |
| Percent probability of survival at end of study ^a | 44 | 28 | 22 | 14 |
| Mean survival (days) ^b | 661 | 625 | 618 | 577 |
| Survival analysis ^c | P<0.001 | P=0.090 | P=0.020 | P<0.001 |

^a Kaplan-Meier determinations

^b Mean of all deaths (uncensored, censored, and terminal sacrifice)

^c The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns.

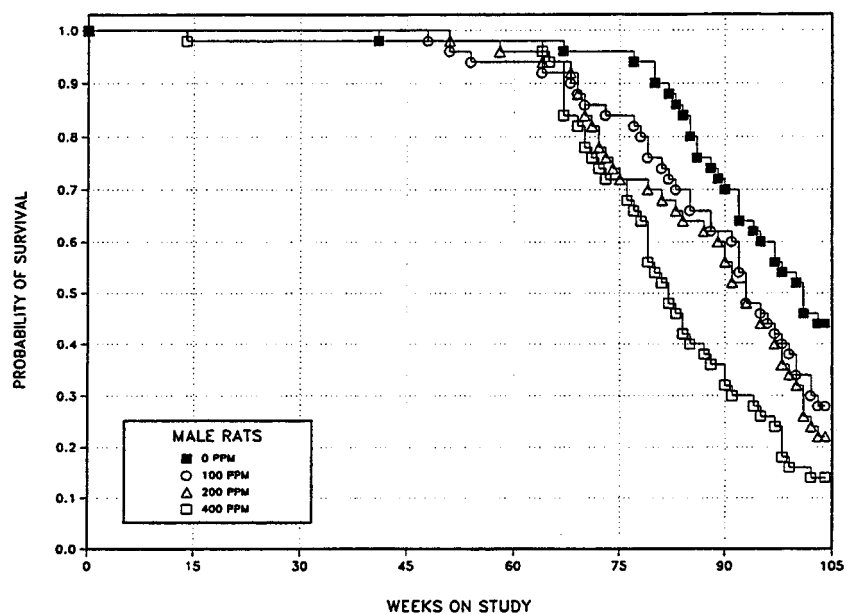


FIGURE 4
Kaplan-Meier Survival Curves for Male Wistar Rats
Exposed to Pyridine in Drinking Water for 2 Years

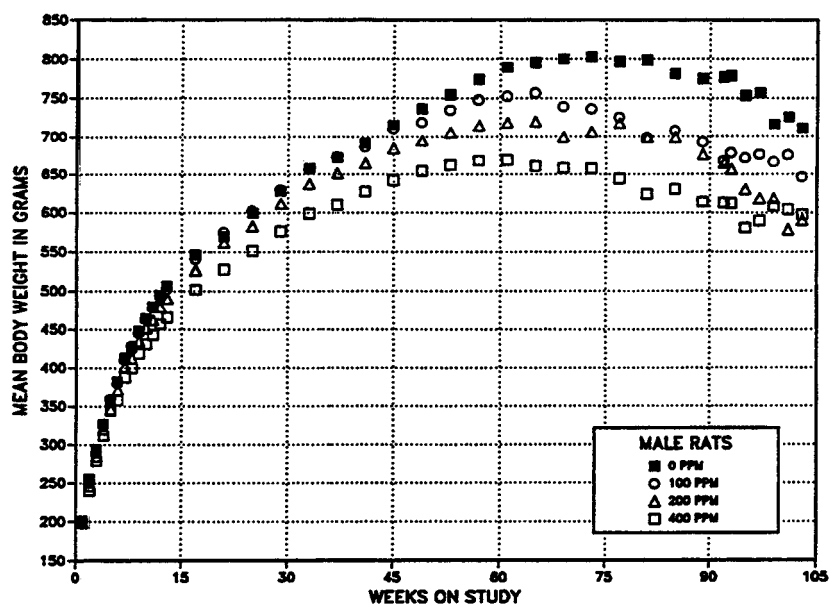


FIGURE 5
Growth Curves for Male Wistar Rats
Exposed to Pyridine in Drinking Water for 2 Years

TABLE 13
Mean Body Weights and Survival of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| Weeks on Study | 0 ppm | | 100 ppm | | | 200 ppm | | | 400 ppm | | |
|-----------------------|----------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 201 | 50 | 198 | 98 | 50 | 199 | 99 | 50 | 198 | 98 | 50 |
| 2 | 255 | 50 | 250 | 98 | 50 | 246 | 97 | 50 | 240 | 94 | 50 |
| 3 | 294 | 50 | 289 | 98 | 50 | 285 | 97 | 50 | 280 | 95 | 50 |
| 4 | 327 | 50 | 326 | 100 | 50 | 321 | 98 | 50 | 312 | 95 | 50 |
| 5 | 357 | 50 | 359 | 101 | 50 | 347 | 97 | 50 | 345 | 96 | 50 |
| 6 | 382 | 50 | 380 | 99 | 50 | 372 | 97 | 50 | 358 | 94 | 50 |
| 7 | 413 | 50 | 411 | 100 | 50 | 402 | 97 | 50 | 388 | 94 | 50 |
| 8 | 426 | 50 | 428 | 101 | 50 | 412 | 97 | 50 | 400 | 94 | 50 |
| 9 | 448 | 50 | 446 | 100 | 50 | 435 | 97 | 50 | 419 | 94 | 50 |
| 10 | 464 | 50 | 463 | 100 | 50 | 452 | 97 | 50 | 431 | 93 | 50 |
| 11 | 479 | 50 | 478 | 100 | 50 | 463 | 97 | 50 | 443 | 93 | 50 |
| 12 | 494 | 50 | 492 | 100 | 50 | 479 | 97 | 50 | 457 | 93 | 50 |
| 13 | 506 | 50 | 503 | 99 | 50 | 490 | 97 | 50 | 466 | 92 | 50 |
| 17 | 546 | 50 | 542 | 99 | 50 | 527 | 97 | 50 | 502 | 92 | 49 |
| 21 | 569 | 50 | 575 | 101 | 50 | 562 | 99 | 50 | 528 | 93 | 49 |
| 25 | 599 | 50 | 602 | 101 | 50 | 583 | 97 | 50 | 552 | 92 | 49 |
| 29 | 627 | 50 | 630 | 100 | 50 | 612 | 98 | 50 | 576 | 92 | 49 |
| 33 | 658 | 50 | 657 | 100 | 50 | 638 | 97 | 50 | 599 | 91 | 49 |
| 37 | 672 | 50 | 673 | 100 | 50 | 651 | 97 | 50 | 610 | 91 | 49 |
| 41 | 691 | 50 | 686 | 99 | 50 | 664 | 96 | 50 | 627 | 91 | 49 |
| 45 | 715 | 49 | 711 | 99 | 50 | 684 | 96 | 50 | 642 | 90 | 49 |
| 49 | 736 | 49 | 719 | 98 | 49 | 695 | 94 | 50 | 654 | 89 | 49 |
| 53 | 755 | 49 | 735 | 97 | 48 | 705 | 93 | 49 | 662 | 88 | 49 |
| 57 | 774 | 49 | 748 | 97 | 47 | 714 | 92 | 49 | 668 | 86 | 49 |
| 61 | 789 | 49 | 753 | 95 | 47 | 718 | 91 | 48 | 669 | 85 | 49 |
| 65 | 795 | 49 | 757 | 95 | 46 | 720 | 91 | 47 | 661 | 83 | 48 |
| 69 | 800 | 48 | 739 | 92 | 45 | 699 | 87 | 46 | 658 | 82 | 42 |
| 73 | 803 | 48 | 736 | 92 | 43 | 706 | 88 | 39 | 657 | 82 | 37 |
| 77 | 797 | 48 | 725 | 91 | 42 | 717 | 90 | 36 | 644 | 81 | 34 |
| 81 | 799 | 45 | 698 | 87 | 38 | 698 | 88 | 34 | 624 | 78 | 27 |
| 85 | 782 | 41 | 707 | 91 | 35 | 699 | 89 | 32 | 630 | 81 | 21 |
| 89 | 775 | 37 | 692 | 89 | 31 | 676 | 87 | 31 | 614 | 79 | 18 |
| 92 | 777 | 35 | 667 | 86 | 29 | 665 | 86 | 26 | 613 | 79 | 15 |
| 93 | 779 | 32 | 678 | 87 | 27 | 657 | 84 | 25 | 612 | 79 | 15 |
| 95 | 753 | 31 | 671 | 89 | 24 | 630 | 84 | 24 | 581 | 77 | 14 |
| 97 | 757 | 30 | 675 | 89 | 22 | 618 | 82 | 22 | 590 | 78 | 13 |
| 99 | 715 | 27 | 666 | 93 | 20 | 618 | 86 | 17 | 609 | 85 | 8 |
| 101 | 725 | 25 | 675 | 93 | 17 | 578 | 80 | 16 | 604 | 83 | 8 |
| 103 | 710 | 23 | 646 | 91 | 15 | 591 | 83 | 12 | 598 | 84 | 7 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 388 | | 386 | 99 | | 377 | 97 | | 364 | 94 | |
| 14-52 | 646 | | 644 | 100 | | 624 | 97 | | 588 | 91 | |
| 53-103 | 770 | | 704 | 91 | | 671 | 87 | | 629 | 82 | |

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the testis, kidney, and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix C for male Wistar rats.

Testis: The incidence of testicular interstitial cell adenoma in rats exposed to 400 ppm was significantly increased compared to controls (Tables 14 and C3). Interstitial cell hyperplasia was observed in control and exposed groups and the incidences were slightly, but not significantly, increased in rats exposed to 200 or 400 ppm (Tables 14 and C4). The appearance of interstitial cells was similar in both hyperplasia and adenoma and the diagnoses were based on size. Some interstitial cell neoplasms nearly replaced normal tissue (Plate 3). Hyperplasia was defined as a proliferation no larger than the diameter of a seminiferous tubule, and interstitial cell adenoma was larger.

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Testis in Male Wistar Rats
in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|----------------------|------------|-----------|-------------|
| Number Examined Microscopically | 50 | 49 | 49 | 50 |
| Interstitial Cell Hyperplasia ^a | 3 (2.3) ^b | 4 (2.0) | 7 (2.3) | 7 (2.9) |
| Adenoma (interstitial cell) | | | | |
| Overall rate ^c | 5/50 (10%) | 6/49 (12%) | 4/49 (8%) | 12/50 (24%) |
| Adjusted rate ^d | 12.3% | 16.9% | 11.9% | 36.6% |
| Terminal rate ^e | 3/22 (14%) | 3/14 (21%) | 1/11 (9%) | 3/7 (43%) |
| First incidence (days) | 592 | 486 | 660 | 464 |
| Poly-3 test ^f | P=0.008 | P=0.404 | P=0.618N | P=0.012 |

^a Number examined microscopically

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

^c Number of animals with neoplasm per number of animals with testis examined microscopically

^d Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^e Observed incidence at terminal kill

^f Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by N.

Kidney: Incidences of renal tubule neoplasms in exposed rats were not significantly different from control incidences in the standard evaluation (Tables 15, C1, and C3). Renal tubule adenomas were observed in control and exposed rats and were similar to those observed in F344/N rats. Cells in renal tubule adenomas were disorganized and had lost their orientation to the tubule basement membrane. One renal tubule carcinoma approximately 5 cm in diameter was observed in the 400 ppm group. This neoplasm had multiple large, solid, irregular proliferations of densely packed, enlarged epithelial cells interspersed with areas of

necrosis and inflammatory cells. In an extended evaluation, kidneys were step sectioned because of the carcinoma in the 400 ppm group, because of increased incidences of renal tubule hyperplasia in 100 ppm males relative to controls (Tables 15 and C4), and for comparison with F344/N male rats. Step sections were prepared from residual wet tissue so that each kidney yielded four additional sections spaced 1 mm apart. Step sectioning did not detect any significant treatment-related increase in incidences of renal tubule hyperplasia, adenoma, or carcinoma.

TABLE 15
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Male Wistar Rats
in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|----------------------|------------|------------|----------|
| Kidney ^a | 50 | 50 | 50 | 50 |
| Single Sections (Standard Evaluation) | | | | |
| Renal Tubule, Hyperplasia ^b | 6 (1.7) ^c | 17** (2.1) | 8 (2.4) | 5 (2.6) |
| Nephropathy | 50 (3.3) | 50 (3.6) | 50 (3.4) | 50 (3.2) |
| Cyst | 21 (2.0) | 31 (2.5) | 19 (2.5) | 16 (2.1) |
| Mineralization | 8 (1.5) | 17 (2.1) | 8 (1.9) | 5 (1.4) |
| Inflammation, Acute | 0 | 2 (3.0) | 0 | 1 (1.0) |
| Renal Tubule, Adenoma (includes multiple) | 2 | 5 | 1 | 2 |
| Renal Tubule, Carcinoma | 0 | 0 | 0 | 1 |
| Renal Tubule, Adenoma or Carcinoma | 2 | 5 | 1 | 3 |
| Step Sections (Extended Evaluation) | | | | |
| Renal Tubule, Hyperplasia | 5 (2.2) | 13 (2.8) | 10 (2.1) | 9 (2.8) |
| Renal Tubule, Oncocytoma | 0 | 1 | 0 | 0 |
| Renal Tubule, Adenoma | 1 | 2 | 4 | 2 |
| Renal Tubule, Carcinoma | 0 | 0 | 1 | 0 |
| Renal Tubule, Adenoma or Carcinoma | 1 | 2 | 5 | 2 |
| Single Sections and Step Sections (Combined) | | | | |
| Renal Tubule, Hyperplasia | 10 (1.8) | 22 (2.5) | 14 (2.4) | 13 (2.8) |
| Renal Tubule, Adenoma | 3 | 6 | 5 | 4 |
| Renal Tubule, Carcinoma | 0 | 0 | 1 | 1 |
| Renal Tubule, Adenoma or Carcinoma | 3 | 6 | 6 | 4 |
| Stomach, Glandular | 49 | 50 | 48 | 48 |
| Mineralization | 8 (2.8) | 25** (2.8) | 16* (2.5) | 6 (2.7) |
| Parathyroid Gland | 48 | 47 | 48 | 47 |
| Hyperplasia | 16 (3.3) | 32** (3.2) | 29** (3.0) | 12 (2.5) |
| Bone | 50 | 50 | 50 | 50 |
| Fibrous Osteodystrophy | 10 (2.8) | 21* (2.8) | 16 (2.9) | 6 (1.7) |

* Significantly different (P 0.05) from the control group by the Poly-3 test

** P 0.01

^a Number examined microscopically

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Hyperplasia consisted of multiple layers rather than the normal single layer of cells, frequently with an increased diameter of the tubule. Severity of hyperplasia depended on the number of layers and the complexity of their patterns. Some had papillary projections, but all maintained their orientation to the basement membrane. Nephropathy was observed in all control and exposed rats (Tables 15 and C4). Nephropathy is a common spontaneous kidney disease that increases in severity with increasing age. Lesions

associated with nephropathy include renal cysts, mineralization of basement membranes, and inflammation of the renal parenchyma (Tables 15 and C4). Nephropathy was moderately severe in control and exposed groups of Wistar males and was considered to be the cause of their high mortality in this study. Probably because the kidney lesions were so severe in the controls, no treatment-related increase in the severity of nephropathy could be detected. However, incidences of extrarenal lesions of kidney disease such

as mineralization in the glandular stomach, parathyroid gland hyperplasia, and fibrous osteodystrophy were generally increased in rats exposed to 100 or 200 ppm compared to controls. These extrarenal lesions suggest that nephropathy was generally more severe in these groups. Kidney disease in 400 ppm rats may have been less severe because of their reduced survival and lower body weights.

Liver: Incidences of hepatocellular neoplasms were not increased in exposed Wistar rats compared to controls, but exposure-related nonneoplastic liver lesions were observed (Tables 16, C1, and C4). Incidences of centrilobular degeneration (cytoplasmic vacuolization) occurred in exposed groups and increased with increasing exposure concentration, and the severities of cytoplasmic vacuolization were slightly increased in the exposed groups. The incidence of centrilobular necrosis was increased in the 400 ppm group compared to

controls. Incidences of fibrosis and periportal fibrosis were increased in the 200 and 400 ppm groups relative to controls. Incidences of pigmentation were increased in each exposed group compared to controls. The incidences of eosinophilic foci decreased compared to controls in rats exposed to 200 or 400 ppm. In general, these liver lesions were more severe in Wistar rats than in F344/N rats.

The overall structure was maintained, but exposed rats tended to have centrilobular hepatocytes that were necrotic or had an altered appearance with an increase in fibrous connective tissue in portal areas and extending downward from the liver capsule. Fibrosis was defined as fibrous connective tissue under the capsule of the liver and extending downward along the vasculature. Periportal fibrosis consisted of bands of fibrous connective tissue in portal areas. Pigmentation consisted of yellow-brown material in macrophages.

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Male Wistar Rats
in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---------------------------------|-----------------------|------------|------------|------------|
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Basophilic Focus ^a | 0 | 0 | 0 | 2 |
| Clear Cell Focus | 15 | 7 | 8 | 8 |
| Eosinophilic Focus | 14 | 12 | 4* | 2** |
| Vacuolization Cytoplasmic | 18 (1.6) ^b | 18 (1.9) | 12 (1.8) | 15 (1.9) |
| Centrilobular, Degeneration | 1 (1.0) | 15** (1.8) | 25** (2.1) | 33** (2.4) |
| Centrilobular, Necrosis | 5 (2.8) | 6 (2.0) | 4 (2.8) | 23** (2.5) |
| Fibrosis | 1 (2.0) | 5 (1.4) | 26** (1.6) | 31** (1.8) |
| Periportal Fibrosis | 0 | 0 | 5* (2.0) | 7** (2.4) |
| Pigmentation | 6 (1.5) | 15* (1.3) | 34** (1.8) | 42** (1.8) |
| Hepatocellular Adenoma | 2 | 0 | 1 | 0 |

* Significantly different (P 0.05) from the control group by the Poly-3 test

** P 0.01

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

MICE

13-WEEK STUDY

One female mouse exposed to 250 ppm died during week 2 (Table 17). Final mean body weights and body weight gains of female mice exposed to 1,000 ppm were significantly less than those of controls; final mean body weights and body weight gains of all other exposed groups were similar to controls. Water consumption by exposed female mice was lower than that by controls at week 1 but was generally slightly higher

than controls at week 13; water consumption by exposed and control male mice was similar. Estimated water consumption declined over the course of the study. Drinking water concentrations of 50, 100, 250, 500, or 1,000 ppm pyridine resulted in average daily doses of 10, 20, 50, 85, or 160 mg/kg for males and 10, 20, 60, 100, or 190 mg/kg for females. There were no treatment-related clinical findings.

TABLE 17
Survival, Body Weights, and Water Consumption of Mice in the 13-Week Drinking Water Study of Pyridine

| Concentration (ppm) | Survival ^a | Mean Body Weight ^b (g) | | | Final Weight Relative to Controls (%) | Water Consumption ^c | |
|------------------------|-----------------------|-----------------------------------|--------------|--------------|--|-----------------------------------|---------|
| | | Initial | Final | Change | | Week 1 | Week 13 |
| Male | | | | | | | |
| 0 | 10/10 | 23.7 ± 0.4 | 39.4 ± 0.9 | 15.7 ± 0.8 | | 395 | 147 |
| 50 | 10/10 | 23.5 ± 0.3 | 38.4 ± 1.1 | 14.9 ± 1.0 | 97 | 349 | 162 |
| 100 | 10/10 | 23.8 ± 0.3 | 39.3 ± 0.9 | 15.4 ± 0.8 | 100 | 318 | 186 |
| 250 | 10/10 | 23.8 ± 0.3 | 40.2 ± 1.1 | 16.3 ± 1.0 | 102 | 364 | 167 |
| 500 | 10/10 | 23.4 ± 0.3 | 39.1 ± 0.8 | 15.8 ± 0.6 | 99 | 336 | 146 |
| 1,000 | 10/10 | 23.7 ± 0.3 | 37.2 ± 0.7 | 13.5 ± 0.6 | 94 | 377 | 121 |
| Female | | | | | | | |
| 0 | 10/10 | 19.0 ± 0.3 | 33.6 ± 1.1 | 14.6 ± 1.0 | | 441 | 149 |
| 50 | 10/10 | 18.7 ± 0.3 | 37.4 ± 1.1 | 18.8 ± 1.1 | 111 | 278 | 147 |
| 100 | 10/10 | 18.9 ± 0.1 | 34.4 ± 0.9 | 15.5 ± 0.8 | 102 | 271 | 192 |
| 250 | 9/10 ^d | 18.7 ± 0.3 | 34.2 ± 1.1 | 15.4 ± 1.0 | 102 | 375 | 214 |
| 500 | 10/10 | 19.4 ± 0.3 | 33.2 ± 0.9 | 13.8 ± 0.8 | 99 | 292 | 172 |
| 1,000 | 10/10 | 18.7 ± 0.2 | 29.7 ± 0.9** | 11.0 ± 0.8** | 88 | 201 | 195 |

** Significantly different (P 0.01) from the control group by Williams' or Dunnett's test

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.

^c Water consumption is expressed as grams of water consumed per kg body weight per day.

^d Week of death: 2

Sperm motility in exposed male mice was decreased relative to controls (Table I3). There were no significant differences in estrous cycle lengths between control and exposed females (Table I4).

Absolute and relative liver weights were significantly increased relative to controls in males exposed to 100 ppm or greater and in 250 and 500 ppm females (Table H3). No histopathologic lesions were observed in the liver despite the increased liver weights, nor were

any chemical-related lesions observed in any other tissue.

Exposure Concentration Selection Rationale: The highest exposure concentration for the 2-year male mouse study was set at 1,000 ppm based on the lack of target organ lesions in the 13-week study. The highest exposure concentration for the 2-year female mouse study was set at 500 ppm based on decreased mean body weight gains relative to controls and decreased water consumption.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 18 and in the Kaplan-Meier survival curves (Figure 6). Survival of exposed males and females was similar to that of the controls.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of exposed males were similar to those of the controls; mean body weights of 250 and 500 ppm females were less than controls (Tables 19

and 20; Figure 7). Water consumption by males exposed to 250 or 500 ppm was generally greater than that by controls during the last year of the study; male mice exposed to 1,000 ppm consumed less water than controls throughout the study (Table L4). Water consumption by exposed females was generally lower than that by controls during the first year of the study, but greater than controls during the second year (Table L5). Drinking water concentrations of 250, 500, or 1,000 ppm pyridine resulted in average daily doses of 35, 65, or 110 mg/kg for male mice and concentrations of 125, 250, or 500 ppm pyridine resulted in average daily doses of 15, 35, or 70 mg/kg for female mice. There were no treatment-related clinical findings.

TABLE 18
Survival of Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|----------|----------|---------|-----------|
| Male | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Accidental deaths ^a | 2 | 1 | 1 | 3 |
| Other ^a | 0 | 0 | 1 | 0 |
| Moribund | 2 | 3 | 3 | 1 |
| Natural deaths | 11 | 18 | 11 | 11 |
| Animals surviving to study termination | 35 | 28 | 34 | 35 |
| Percent probability of survival at end of study ^b | 73 | 57 | 71 | 75 |
| Mean survival (days) ^c | 685 | 660 | 670 | 656 |
| Survival analysis ^d | P=0.507N | P=0.138 | P=0.928 | P=1.000N |
| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
| Female | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Accidental deaths ^a | 3 | 6 | 4 | 5 |
| Moribund | 3 | 2 | 3 | 5 |
| Natural deaths | 12 | 12 | 21 | 11 |
| Animals surviving to study termination | 32 | 30 | 22 | 29 |
| Percent probability of survival at end of study | 68 | 68 | 48 | 65 |
| Mean survival (days) | 671 | 640 | 638 | 624 |
| Survival analysis | P=0.487 | P=1.000N | P=0.090 | P=0.755 |

^a Censored from survival analyses

^b Kaplan-Meier determinations

^c Mean of all deaths (uncensored, censored, and terminal sacrifice)

^d The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by N.

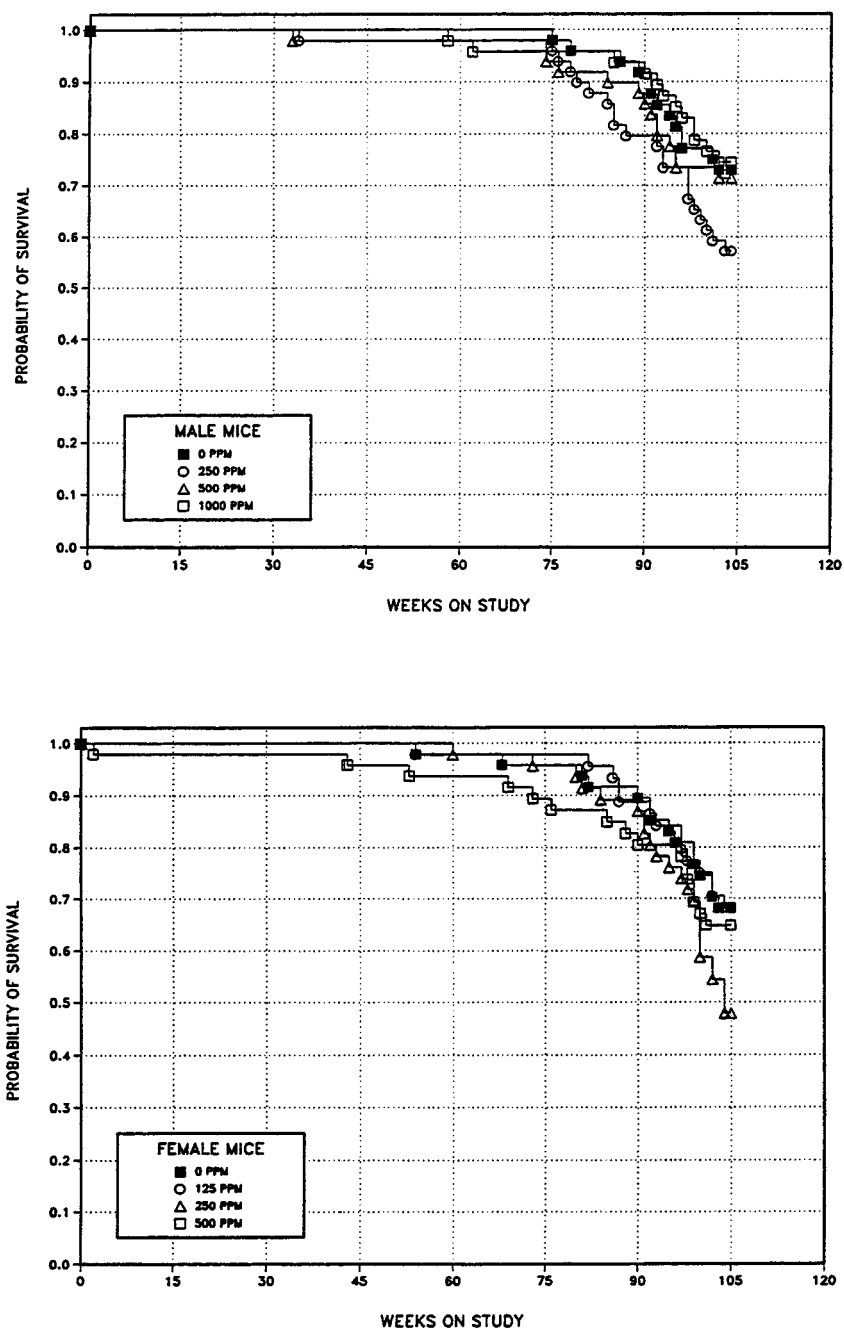


FIGURE 6
Kaplan-Meier Survival Curves for Male and Female Mice
Exposed to Pyridine in Drinking Water for 2 Years

TABLE 19
Mean Body Weights and Survival of Male Mice in the 2-Year Drinking Water Study of Pyridine

| Weeks on Study | 0 ppm | | 250 ppm | | | 500 ppm | | | 1,000 ppm | | |
|-----------------------|----------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 26.1 | 50 | 25.9 | 99 | 50 | 25.8 | 99 | 50 | 25.8 | 99 | 50 |
| 2 | 27.6 | 50 | 27.4 | 99 | 49 | 27.3 | 99 | 49 | 26.6 | 96 | 49 |
| 3 | 29.2 | 50 | 28.7 | 98 | 49 | 29.0 | 99 | 49 | 28.4 | 97 | 48 |
| 4 | 30.9 | 50 | 30.5 | 99 | 49 | 30.7 | 99 | 49 | 30.1 | 97 | 48 |
| 5 | 32.8 | 50 | 32.3 | 99 | 49 | 32.2 | 98 | 49 | 30.6 | 93 | 48 |
| 6 | 33.9 | 50 | 34.2 | 101 | 49 | 33.5 | 99 | 49 | 32.0 | 94 | 48 |
| 7 | 35.4 | 50 | 35.4 | 100 | 49 | 35.3 | 100 | 49 | 33.9 | 96 | 48 |
| 8 | 37.6 | 50 | 37.1 | 99 | 49 | 36.7 | 98 | 49 | 35.6 | 95 | 48 |
| 9 | 38.7 | 50 | 37.9 | 98 | 49 | 37.7 | 97 | 49 | 36.5 | 94 | 48 |
| 10 | 39.6 | 50 | 40.1 | 101 | 49 | 39.8 | 101 | 49 | 37.7 | 95 | 47 |
| 11 | 40.6 | 50 | 41.0 | 101 | 49 | 41.0 | 101 | 49 | 38.8 | 96 | 47 |
| 12 | 41.8 | 50 | 42.3 | 101 | 49 | 41.7 | 100 | 49 | 39.8 | 95 | 47 |
| 13 | 42.4 | 50 | 42.9 | 101 | 49 | 42.7 | 101 | 49 | 40.6 | 96 | 47 |
| 17 | 47.0 | 50 | 46.2 | 98 | 49 | 45.9 | 98 | 49 | 43.5 | 93 | 47 |
| 21 | 48.1 | 49 | 48.3 | 100 | 49 | 47.4 | 99 | 49 | 45.2 | 94 | 47 |
| 25 | 50.0 | 49 | 49.6 | 99 | 49 | 49.9 | 100 | 49 | 47.5 | 95 | 47 |
| 29 | 49.6 | 49 | 50.8 | 102 | 49 | 51.3 | 103 | 49 | 48.5 | 98 | 47 |
| 33 | 51.6 | 49 | 51.7 | 100 | 49 | 51.1 | 99 | 49 | 50.0 | 97 | 47 |
| 37 | 53.2 | 49 | 52.9 | 99 | 48 | 53.0 | 100 | 48 | 51.8 | 97 | 47 |
| 41 | 54.5 | 49 | 53.8 | 99 | 48 | 53.7 | 99 | 48 | 52.5 | 96 | 47 |
| 45 | 54.1 | 49 | 53.9 | 100 | 48 | 54.4 | 101 | 48 | 52.7 | 97 | 47 |
| 49 | 55.3 | 49 | 54.6 | 99 | 48 | 55.4 | 100 | 48 | 53.4 | 97 | 47 |
| 53 | 55.4 | 49 | 55.6 | 100 | 48 | 56.2 | 101 | 48 | 54.7 | 99 | 47 |
| 57 | 55.2 | 49 | 55.4 | 100 | 48 | 56.0 | 101 | 48 | 54.0 | 98 | 47 |
| 61 | 55.2 | 49 | 56.1 | 102 | 48 | 56.4 | 102 | 48 | 54.2 | 98 | 46 |
| 65 | 54.4 | 49 | 56.3 | 104 | 48 | 56.1 | 103 | 48 | 54.1 | 99 | 45 |
| 69 | 55.1 | 49 | 56.5 | 103 | 48 | 55.5 | 101 | 48 | 54.4 | 99 | 45 |
| 73 | 54.4 | 49 | 56.6 | 104 | 48 | 53.9 | 99 | 48 | 54.1 | 99 | 45 |
| 77 | 52.8 | 48 | 55.1 | 104 | 46 | 52.2 | 99 | 45 | 52.4 | 99 | 45 |
| 81 | 51.4 | 47 | 53.7 | 105 | 44 | 50.2 | 98 | 45 | 49.2 | 96 | 45 |
| 85 | 49.2 | 46 | 51.5 | 105 | 42 | 47.8 | 97 | 44 | 47.3 | 96 | 45 |
| 89 | 46.6 | 45 | 49.7 | 107 | 39 | 45.8 | 98 | 44 | 45.6 | 98 | 44 |
| 93 | 45.5 | 41 | 46.4 | 102 | 37 | 44.7 | 98 | 39 | 43.7 | 96 | 42 |
| 97 | 43.8 | 37 | 43.6 | 100 | 36 | 42.9 | 98 | 36 | 41.8 | 95 | 39 |
| 99 | 44.5 | 37 | 43.5 | 98 | 32 | 42.7 | 96 | 36 | 41.2 | 93 | 37 |
| 101 | 44.2 | 37 | 41.9 | 95 | 30 | 41.6 | 94 | 36 | 40.6 | 92 | 36 |
| 103 | 44.0 | 35 | 41.2 | 94 | 28 | 40.0 | 91 | 35 | 39.8 | 91 | 35 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 35.1 | | 35.1 | 100 | | 34.9 | 99 | | 33.6 | 96 | |
| 14-52 | 51.5 | | 51.3 | 100 | | 51.3 | 100 | | 49.5 | 96 | |
| 53-103 | 50.1 | | 50.9 | 102 | | 49.5 | 99 | | 48.5 | 97 | |

TABLE 20
Mean Body Weights and Survival of Female Mice in the 2-Year Drinking Water Study of Pyridine

| Weeks on Study | 0 ppm | | 125 ppm | | | 250 ppm | | | 500 ppm | | |
|-----------------------|----------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 20.8 | 50 | 20.7 | 100 | 50 | 20.6 | 99 | 50 | 20.5 | 99 | 50 |
| 2 | 21.8 | 50 | 21.4 | 98 | 49 | 21.6 | 99 | 49 | 21.5 | 99 | 50 |
| 3 | 23.2 | 50 | 22.8 | 98 | 49 | 22.8 | 98 | 49 | 22.6 | 97 | 47 |
| 4 | 24.1 | 50 | 24.0 | 100 | 47 | 23.9 | 99 | 49 | 23.7 | 98 | 47 |
| 5 | 25.5 | 50 | 25.3 | 99 | 47 | 25.5 | 100 | 49 | 25.6 | 100 | 47 |
| 6 | 26.7 | 50 | 26.5 | 99 | 47 | 26.3 | 99 | 48 | 26.9 | 101 | 47 |
| 7 | 28.2 | 50 | 28.4 | 101 | 47 | 28.8 | 102 | 47 | 28.5 | 101 | 47 |
| 8 | 29.6 | 50 | 29.9 | 101 | 47 | 29.8 | 101 | 47 | 30.0 | 101 | 47 |
| 9 | 31.1 | 50 | 30.1 | 97 | 47 | 30.8 | 99 | 47 | 30.4 | 98 | 47 |
| 10 | 31.7 | 49 | 32.0 | 101 | 47 | 32.7 | 103 | 47 | 32.9 | 104 | 47 |
| 11 | 33.3 | 49 | 33.2 | 100 | 47 | 33.7 | 101 | 47 | 33.7 | 101 | 47 |
| 12 | 34.1 | 49 | 34.2 | 100 | 47 | 35.2 | 103 | 47 | 35.1 | 103 | 47 |
| 13 | 35.8 | 49 | 35.5 | 99 | 47 | 36.5 | 102 | 47 | 36.3 | 101 | 47 |
| 17 | 40.2 | 49 | 39.4 | 98 | 47 | 40.5 | 101 | 47 | 40.4 | 101 | 47 |
| 21 | 41.1 | 49 | 40.0 | 97 | 47 | 41.6 | 101 | 47 | 41.4 | 101 | 47 |
| 25 | 45.9 | 48 | 44.2 | 96 | 47 | 45.8 | 100 | 47 | 45.1 | 98 | 47 |
| 29 | 45.7 | 48 | 44.9 | 98 | 46 | 47.2 | 103 | 46 | 46.5 | 102 | 46 |
| 33 | 49.1 | 48 | 47.7 | 97 | 46 | 49.5 | 101 | 46 | 48.7 | 99 | 46 |
| 37 | 51.0 | 48 | 49.4 | 97 | 46 | 51.0 | 100 | 46 | 50.1 | 98 | 46 |
| 41 | 53.1 | 48 | 51.1 | 96 | 46 | 53.2 | 100 | 46 | 52.0 | 98 | 46 |
| 45 | 54.0 | 48 | 52.5 | 97 | 46 | 54.1 | 100 | 46 | 52.2 | 97 | 45 |
| 49 | 56.2 | 48 | 54.5 | 97 | 46 | 55.6 | 99 | 46 | 54.4 | 97 | 45 |
| 53 | 56.9 | 48 | 55.6 | 98 | 46 | 57.1 | 100 | 46 | 55.5 | 98 | 45 |
| 57 | 58.2 | 47 | 56.4 | 97 | 45 | 58.0 | 100 | 46 | 56.8 | 98 | 44 |
| 61 | 59.5 | 47 | 57.9 | 97 | 44 | 59.3 | 100 | 45 | 58.1 | 98 | 44 |
| 65 | 59.9 | 47 | 58.5 | 98 | 44 | 61.0 | 102 | 45 | 58.6 | 98 | 43 |
| 69 | 61.6 | 46 | 59.3 | 96 | 44 | 62.1 | 101 | 45 | 58.2 | 95 | 43 |
| 73 | 62.8 | 46 | 60.2 | 96 | 44 | 62.2 | 99 | 45 | 58.0 | 92 | 42 |
| 77 | 63.3 | 46 | 61.0 | 96 | 44 | 61.9 | 98 | 44 | 55.4 | 88 | 40 |
| 81 | 62.2 | 45 | 60.3 | 97 | 43 | 60.4 | 97 | 43 | 51.6 | 83 | 40 |
| 85 | 61.1 | 43 | 58.6 | 96 | 42 | 58.8 | 96 | 41 | 48.7 | 80 | 39 |
| 89 | 60.0 | 43 | 58.0 | 97 | 39 | 54.4 | 91 | 41 | 45.8 | 76 | 37 |
| 93 | 57.4 | 40 | 56.3 | 98 | 38 | 50.9 | 89 | 37 | 43.7 | 76 | 36 |
| 97 | 55.7 | 38 | 52.7 | 95 | 37 | 47.1 | 85 | 35 | 40.2 | 72 | 36 |
| 99 | 56.1 | 37 | 53.3 | 95 | 34 | 46.1 | 82 | 33 | 40.1 | 72 | 33 |
| 101 | 55.5 | 35 | 52.5 | 95 | 33 | 42.8 | 77 | 27 | 39.9 | 72 | 30 |
| 103 | 56.1 | 33 | 50.7 | 90 | 31 | 41.2 | 73 | 25 | 39.1 | 70 | 29 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 28.1 | | 28.0 | 100 | | 28.3 | 101 | | 28.3 | 101 | |
| 14-52 | 48.5 | | 47.1 | 97 | | 48.7 | 100 | | 47.9 | 99 | |
| 53-103 | 59.1 | | 56.8 | 96 | | 54.9 | 93 | | 50.0 | 85 | |

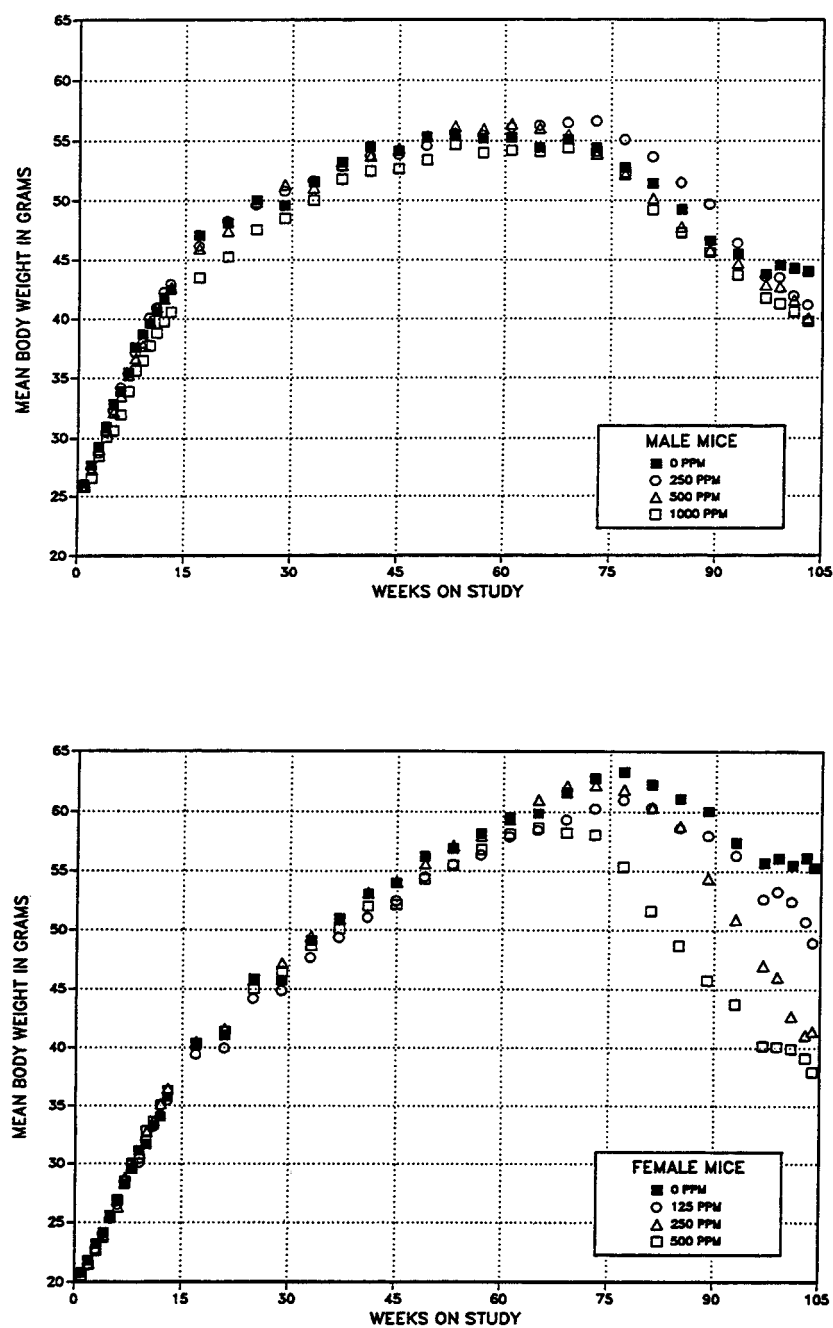


FIGURE 7
Growth Curves for Male and Female Mice
Exposed to Pyridine in Drinking Water for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the liver and other organs. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix D for male mice and Appendix E for female mice.

Liver: Hepatocellular neoplasms in male and female mice were clearly related to pyridine exposure. Incidences of hepatocellular adenoma were significantly increased relative to controls in 250 ppm males and females and 1,000 ppm males (Tables 21, D3, and E3). Incidences of hepatocellular carcinoma and hepatoblastoma were significantly increased relative to controls in all exposed groups of males and females except for the incidence of hepatoblastoma in 125 ppm females. Incidences of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) were significantly increased in all exposed male groups and in 250 and 500 ppm females. The incidences of hepatocellular neoplasms in exposed males and females generally exceeded the historical control ranges (Tables 21, D4, and E4). Incidences of hepatoblastoma in control and exposed males and females exceeded the historical control range. While the control incidence of liver neoplasms in female mice was among the highest historically, almost all neoplasms were adenomas.

Almost every exposed animal that lived one year or more developed one or multiple liver neoplasms, often carcinomas or hepatoblastomas, with many metastasizing to the lung. Hepatocellular neoplasms in exposed mice were similar to those that occur spontaneously. A hepatocellular adenoma was typically a discrete proliferation of hepatocytes that compressed adjacent tissue and had uneven growth patterns resulting in a slightly abnormal architecture (Plate 4). Hepatocellular carcinomas had a distinctly altered structure, cells were often pleomorphic, and the boundary with the adjacent parenchyma was often unclear (Plate 5). Hepatoblastomas had very poorly differentiated cells (frequently basophilic, small, and spindle-

shaped) that had markedly altered architectures of solid sheets, rosettes, ribbons, or trabeculae (Plate 6). Hepatoblastomas nearly always were found in the midst of a hepatocellular carcinoma, but unless there was a clearly separate hepatocellular carcinoma, only the diagnosis of hepatoblastoma was made.

Some of the hepatocellular carcinomas and many of the hepatoblastomas had areas of necrosis, and metastatic lesions were noted in the lungs or, less frequently, in the lymph nodes or adjacent abdominal organs (Tables D1 and E1). There were no treatment-related increased incidences of foci of cellular alteration relative to controls (Tables 21, D5, and E5). Foci of cellular alteration were contiguous hepatocytes of less than a lobule up to approximately four lobules; they varied tinctorially from the rest of the liver but tended to merge imperceptibly with the adjacent parenchyma.

Liver neoplasms from control mice, 500 ppm females, and 1,000 ppm males were stained for p53 protein and compared to a control carcinoma from the mammary gland of a p53 positive transgenic mouse. All of the liver sections tested were negative for p53 protein.

Other Organs: Incidences of hematopoietic cell proliferation in the spleen were increased relative to controls in exposed males (0 ppm, 13/49; 250 ppm, 30/50; 500 ppm, 26/47; 1,000 ppm, 23/49; Table D5) and females (0 ppm, 29/49; 125 ppm, 27/50; 250 ppm, 32/48; 500 ppm, 39/49; Table E5) and may have been compensation for destruction of blood cells in the altered vasculature of the hepatic neoplasms and their metastases. Increased incidences of follicular cell hyperplasia in the thyroid gland of exposed males and females were not accompanied by a significant increased incidence of thyroid gland neoplasms relative to controls (males: 8/49, 14/50, 20/49, 12/50; females: 14/50, 21/50, 22/50, 23/50; Tables D1, D5, E1, and E5). An apparent decrease in the incidences of hyaline degeneration in the respiratory epithelium of exposed males and females (males: 20/50, 10/49, 15/49, 2/50; females: 26/50, 16/50, 12/47, 13/50) and increases in incidences of hyaline degeneration in the olfactory epithelium of exposed females (19/50, 27/50, 35/47, 36/50) compared to controls were of unknown biological significance. Hyaline degeneration in the nasal epithelium is an accumulation of eosinophilic material in the cytoplasm and a common alteration in aging mice.

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice
in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|-------------|--------------|--------------|--------------|
| Male | | | | |
| Number Examined Microscopically | 50 | 50 | 49 | 50 |
| Basophilic Focus ^a | 3 | 1 | 0 | 0 |
| Eosinophilic Focus | 19 | 22 | 18 | 15 |
| Mixed Cell Focus | 4 | 2 | 1 | 1 |
| Hepatocellular Adenoma, Multiple | 16 | 29* | 29* | 28* |
| Hepatocellular Adenoma (includes multiple) ^b | | | | |
| Overall rate ^c | 29/50 (58%) | 40/50 (80%) | 34/49 (69%) | 39/50 (78%) |
| Adjusted rate ^d | 63.2% | 88.0% | 75.7% | 84.9% |
| Terminal rate ^e | 24/35 (69%) | 27/28 (96%) | 27/34 (79%) | 31/35 (89%) |
| First incidence (days) | 520 | 522 | 513 | 406 |
| Poly-3 test ^f | P=0.031 | P=0.003 | P=0.134 | P=0.011 |
| Hepatocellular Carcinoma, Multiple | 3 | 19** | 26** | 18** |
| Hepatocellular Carcinoma (includes multiple) ^g | | | | |
| Overall rate | 15/50 (30%) | 35/50 (70%) | 41/49 (84%) | 40/50 (80%) |
| Adjusted rate | 32.3% | 78.7% | 89.9% | 85.1% |
| Terminal rate | 9/35 (26%) | 23/28 (82%) | 32/34 (94%) | 28/35 (80%) |
| First incidence (days) | 574 | 522 | 513 | 406 |
| Poly-3 test | P<0.001 | P<0.001 | P<0.001 | P<0.001 |
| Hepatoblastoma, Multiple | 1 | 4 | 6* | 2 |
| Hepatoblastoma (includes multiple) ^h | | | | |
| Overall rate | 2/50 (4%) | 18/50 (36%) | 22/49 (45%) | 15/50 (30%) |
| Adjusted rate | 4.5% | 41.2% | 49.8% | 34.4% |
| Terminal rate | 2/35 (6%) | 11/28 (39%) | 17/34 (50%) | 13/35 (37%) |
| First incidence (days) | 722 (T) | 549 | 514 | 624 |
| Poly-3 test | P=0.005 | P<0.001 | P<0.001 | P<0.001 |
| Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma ⁱ | | | | |
| Overall rate | 38/50 (76%) | 47/50 (94%) | 46/49 (94%) | 47/50 (94%) |
| Adjusted rate | 80.1% | 98.9% | 98.5% | 100.0% |
| Terminal rate | 29/35 (83%) | 28/28 (100%) | 34/34 (100%) | 35/35 (100%) |
| First incidence (days) | 520 | 522 | 513 | 406 |
| Poly-3 test | P<0.001 | P=0.002 | P=0.003 | P<0.001 |

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice
in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|--|-------------|-------------|--------------|--------------|
| Female (continued) | | | | |
| Number Examined Microscopically | 49 | 50 | 50 | 50 |
| Basophilic Focus | 1 | 0 | 0 | 0 |
| Eosinophilic Focus | 17 | 12 | 14 | 9 |
| Mixed Cell Focus | 5 | 4 | 3 | 0 |
| Hepatocellular Adenoma, Multiple | 24 | 34* | 37** | 30 |
| Hepatocellular Adenoma (includes multiple) ^j | | | | |
| Overall rate | 37/49 (76%) | 39/50 (78%) | 43/50 (86%) | 34/50 (68%) |
| Adjusted rate | 82.5% | 87.9% | 97.3% | 79.1% |
| Terminal rate | 27/32 (84%) | 27/30 (90%) | 22/22 (100%) | 23/29 (79%) |
| First incidence (days) | 554 | 419 | 509 | 430 |
| Poly-3 test | P=0.372N | P=0.336 | P=0.015 | P=0.442N |
| Hepatocellular Carcinoma, Multiple | 3 | 11* | 14** | 30** |
| Hepatocellular Carcinoma (includes multiple) ^k | | | | |
| Overall rate | 13/49 (27%) | 23/50 (46%) | 33/50 (66%) | 41/50 (82%) |
| Adjusted rate | 29.8% | 55.0% | 78.1% | 97.1% |
| Terminal rate | 8/32 (25%) | 18/30 (60%) | 20/22 (91%) | 29/29 (100%) |
| First incidence (days) | 476 | 573 | 556 | 479 |
| Poly-3 test | P<0.001 | P=0.014 | P<0.001 | P<0.001 |
| Hepatoblastoma, Multiple | 0 | 0 | 3 | 4 |
| Hepatoblastoma (includes multiple) ^l | | | | |
| Overall rate | 1/49 (2%) | 2/50 (4%) | 9/50 (18%) | 16/50 (32%) |
| Adjusted rate | 2.4% | 4.9% | 21.6% | 39.6% |
| Terminal rate | 1/32 (3%) | 1/30 (3%) | 3/22 (14%) | 12/29 (41%) |
| First incidence (days) | 729 (T) | 599 | 564 | 510 |
| Poly-3 test | P<0.001 | P=0.493 | P=0.007 | P<0.001 |
| Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma ^m | | | | |
| Overall rate | 41/49 (84%) | 42/50 (84%) | 45/50 (90%) | 44/50 (88%) |
| Adjusted rate | 89.9% | 94.6% | 99.6% | 99.5% |
| Terminal rate | 29/32 (91%) | 29/30 (97%) | 22/22 (100%) | 29/29 (100%) |
| First incidence (days) | 476 | 419 | 509 | 430 |
| Poly-3 test | P=0.009 | P=0.323 | P=0.042 | P=0.045 |

* Significantly different (P 0.05) from the control group by the Poly-3 test

** P 0.01

^a Number of animals with lesion

^b Historical incidence for 2-year drinking water studies with untreated control groups (mean ± standard deviation): 179/289 (61.9% ± 9.1%); range, 47%-70%

^c Number of animals with neoplasm per number of animals with liver examined microscopically

^d Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^e Observed incidence at terminal kill

^f Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by N.

^g Historical incidence: 80/289 (27.7% ± 11.7%); range, 10%-42%

^h Historical incidence: 9/289 (3.1% ± 5.0%); range, 0%-12%

ⁱ Historical incidence: 212/289 (73.4% ± 11.7%); range, 53%-81%

^j Historical incidence: 150/289 (51.9% ± 20.8%); range, 26%-80%

^k Historical incidence: 55/289 (19.0% ± 13.7%); range, 8%-42%

^l Historical incidence: 0/289

^m Historical incidence: 173/289 (59.9% ± 21.3%); range, 32%-82%

GENETIC TOXICOLOGY

Pyridine (100-10,000 µg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes (Haworth *et al.*, 1983; Table F1). Further, no significant increase in mutation frequencies was observed in L5178Y mouse lymphoma cells tested with and without S9 metabolic activation (McGregor *et al.*, 1988; Table F2). In cytogenetic tests with cultured Chinese hamster ovary cells, pyridine did not induce sister chromatid exchanges (Table F3) or chromosomal aberrations (Table F4), with or without S9. At the highest viable dose (1,673 µg/mL) tested for sister chromatid exchange induction in the absence of S9, pyridine induced marked cell cycle delay, and an extended culture time (31 hours) was used to allow sufficient cells to accumulate for analysis.

Pyridine was tested on three separate occasions in two different laboratories for induction of sex-linked recessive lethal mutations in adult male *Drosophila melanogaster* (Valencia *et al.*, 1985; Mason *et al.*, 1992; Foureman *et al.*, 1994; Table F5), and mixed results were obtained. In the first experiment (Valencia *et al.*, 1985), administration of pyridine by injection (7,000 ppm in aqueous 0.7% saline solution) gave negative ($P=0.225$) results, but feeding (600 or 700 ppm pyridine in aqueous 5% sucrose) produced an increase in recessive lethal mutations that was considered to be equivocal ($P=0.043$). A second experiment performed in the same laboratory using both injection (500 ppm) and feeding (729 ppm) yielded negative

results (Foureman *et al.*, 1994). In the third experiment (Mason *et al.*, 1992) performed in a second laboratory, results of a feeding (500 ppm) experiment were negative ($P=0.998$), but administration of pyridine by injection (4,300 ppm) induced a significant increase in the frequency of sex-linked recessive lethal mutations ($P=0.008$). Overall, pyridine was considered to be negative in sex-linked recessive lethal tests when administered by feeding and equivocal when administered by injection. This positive result in the sex-linked recessive lethal test led to the performance of a test for induction of reciprocal translocations in germ cells of treated male *Drosophila melanogaster* (Mason *et al.*, 1992; Table F6); results of this test were negative.

In vivo assays for chromosomal effects were conducted with male mice. No induction of chromosomal aberrations (Table F7) was noted in bone marrow cells at either of two sampling times (400-600 mg/kg pyridine; single injection), and no increase in the frequency of micronucleated polychromatic erythrocytes (Table F8) was noted in bone marrow after intraperitoneal injection of pyridine (up to 500 mg/kg administered three times at 24-hour intervals).

In summary, with the exception of the single positive result obtained in a *Drosophila melanogaster* sex-linked recessive lethal assay, no indication of mutagenic activity was seen with pyridine in a variety of *in vitro* and *in vivo* assays for gene mutation and chromosomal damage.



PLATE 1

Kidney from a male F344/N rat exposed to 400 ppm pyridine in drinking water for 2 years. Hyperplasia of the renal tubular epithelium are indicated by asterisks. Note that multiple cross sections of the tubule are distended with epithelial cells. H&E; 66×

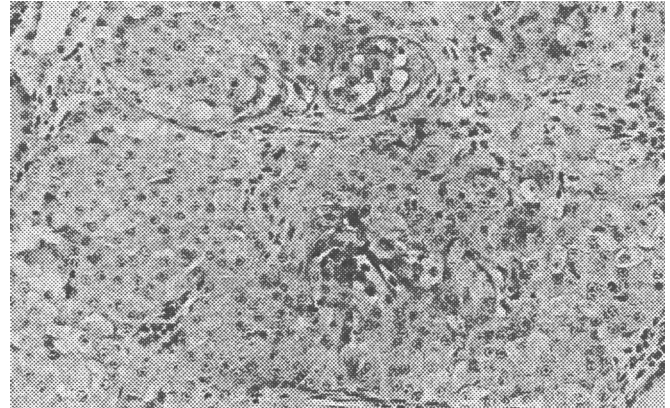


PLATE 2

Kidney from a male F344/N rat exposed to 400 ppm pyridine in drinking water for 2 years. Note the renal tubule adenoma consisting of a larger cluster of cells than a hyperplasia and resulting in a loss of tubular structure. H&E; 66×

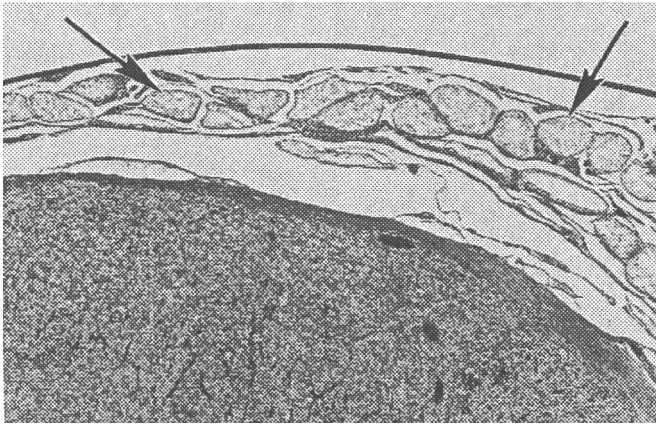


PLATE 3

Testis from a male Wistar rat exposed to 400 ppm pyridine in drinking water for 2 years. A large interstitial cell adenoma compresses degenerate seminiferous tubules (arrows). H&E; 13×

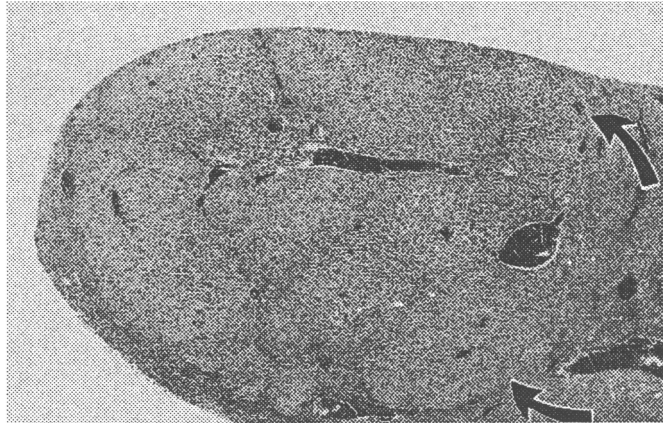


PLATE 4

Liver from a female B6C3F₁ mouse exposed to 250 ppm pyridine in the drinking water for 2 years. A large hepatocellular adenoma compresses (arrows) the parenchyma. H&E; 8×

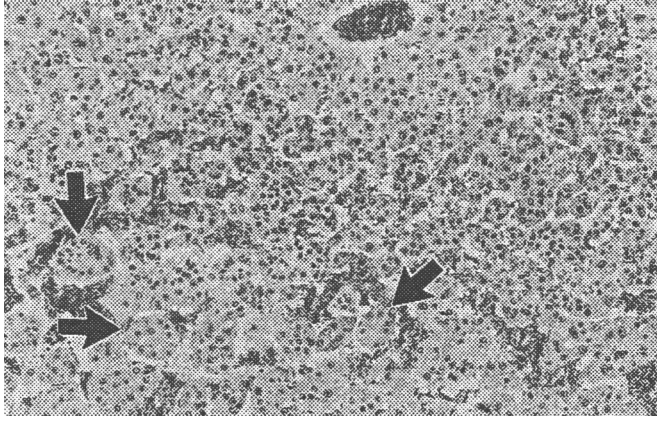


PLATE 5

Liver from a male B6C3F₁ mouse exposed to 1,000 ppm pyridine for 2 years. A hepatocellular carcinoma with a trabecular pattern shows clusters of hepatocytes (arrows) rather than the normal lobular architecture. H&E; 33×

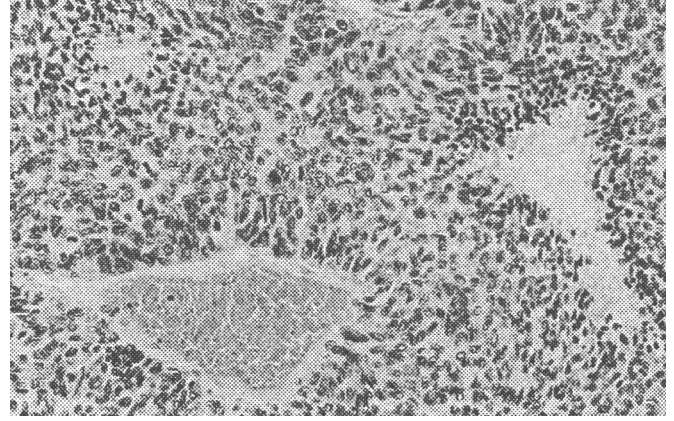


PLATE 6

Liver from a male B6C3F₁ mouse exposed to 500 ppm pyridine for 2 years. Note the small spindle-shaped cells of a hepatoblastoma rather than normal polyhedral hepatocytes. H&E; 66×

DISCUSSION AND CONCLUSIONS

Pyridine was nominated by the National Cancer Institute for toxicity and carcinogenicity studies because of its large annual production and the potential for human exposure. No previous 2-year carcinogenesis bioassays for pyridine have been reported in the literature. Pyridine is used in a variety of industrial processes including the production of pesticides and herbicides, and it is found as a natural component in some foods.

The target organs in the 13-week drinking water studies included the liver and kidney in male F344/N and Wistar rats and the liver in female F344/N rats. Decreased water consumption and/or body weight effects were observed in 1,000 ppm mice in the 13-week study, but no target organ lesions were observed. The liver and kidney have previously been reported as target organs in rats administered pyridine in feed at 0.34% to 1.0% for up to 4 months (Baxter, 1948). Liver toxicity was observed in Sprague-Dawley rats administered 50 mg pyridine/kg body weight per day by oral gavage for 13 weeks (Anderson, 1987).

Kidney: In a number of NTP studies with F344/N rats the kidney is the site of a spectrum of lesions. Some lesions may be spontaneous and age-related, particularly chronic, progressive nephropathy. Others result from direct or indirect effects of the test chemical. In 13-week studies small, eosinophilic hyaline droplets are sometimes seen within the cytoplasm of the epithelial cells of the P2 segment of the renal tubule. These protein droplets typically contain a low molecular weight protein (α 2u-globulin), which is synthesized under the control of androgens and growth hormones. The α 2u-globulin is filtered in the glomerulus; approximately half is reabsorbed by the proximal tubule epithelium and half is excreted in the urine (Neuhauss *et al.*, 1981). Normally only small amounts of the reabsorbed protein are visible as hyaline droplets as it is degraded by enzymes in the tubule epithelium. Some chemicals (inducers) reversibly combine with reabsorbed α 2u-globulin and make it more resistant to enzymatic degradation, resulting in protein material

accumulation in the renal tubule epithelium (Lehman-McKeeman *et al.*, 1989). It is theorized that phagosomal accumulation of the proteinaceous material can result in accelerated renal tubule epithelium cell death.

Hyaline droplet nephropathy or α 2u-globulin nephropathy are terms used to describe the renal changes associated with α 2u-globulin inducers. In addition to accumulation of hyaline droplets, other microscopic changes consistent with hyaline droplet nephropathy include granular cast within tubular lumens of the outer medulla and exacerbated nephropathy. The casts are thought to consist of aggregates of sloughed necrotic cells from the affected P2 segment. Less specific, but generally considered a component of the spectrum of renal changes brought on by α 2u-globulin, is an exacerbation of the spontaneous chronic progressive nephropathy. Other findings generally associated with α 2u-globulin in 2-year studies include an increase in linear foci of mineralization within the renal medulla and an increase in proliferative lesions (including neoplasms) of the renal tubules. It is theorized that phagolysosomal accumulation of proteinaceous matter leads to an overload phenomenon, resulting in accelerated renal tubule cell death with subsequent regeneration by increased cell replication. Increased cell replication is thought to be lined with eventual development of renal tubule neoplasms (USEPA, 1991).

In male F344/N rats from the 13-week study of pyridine, kidney changes consistent with α 2u-globulin inducers were observed in the 1,000 ppm group and to a lesser extent in the 500 ppm group. These changes included a very subtle increase in the amount of hyaline droplets which appeared positive for α 2u-globulin by immunohistochemistry and one to three small granular casts in 1,000 and 500 ppm males; at the next lowest exposure concentration (250 ppm) no changes were observed consistent with hyaline droplet nephropathy. In the 2-year studies there was a marginal increase in the incidence of renal tubule adenomas in the 400 ppm male F344/N rats. An extended evaluation of the entire

kidney by step sectioning confirmed a significant exposure-related increase in the incidences of renal tubule adenomas in this group. Slight increases in the incidences of renal tubule hyperplasia were also observed for 400 ppm male F344/N rats and 100 ppm Wistar rats.

Establishing causation between neoplastic outcome and the α 2u-globulin response in male rats requires demonstration of similar exposure-response relationships between renal tubule neoplasm incidence and α 2u-globulin accumulation (as determined by histopathology and immunohistochemistry), reversible binding of the chemical or its metabolite to α 2u-globulin, and sustained cell proliferation in the renal cortex. In studies in which the association between hyaline droplet nephropathy and neoplasm development was clearly demonstrated, the severities of hyaline droplets and granular casts exceeded those observed in the present study. Moreover, the rat renal tubule neoplastic response occurred mainly at an exposure concentration (400 ppm) lower than the concentration at which only subtle lesions characteristic of α 2u-globulin inducers were observed (500 ppm). Additionally, six renal tubule neoplasms occurred in the 200 ppm group compared with two in the control group. No evidence of α 2u-globulin nephropathy was observed at 250 ppm or below in the 13-week studies. In the F344/N rats in this study of pyridine, there was no significant exacerbation of nephropathy after 2 years, nor were there any significant increases in the incidences of parathyroid gland hyperplasia or fibrous osteodystrophy, two common changes in NTP studies with chemical-exacerbated chronic progressive nephropathy. There were also no liner foci of mineralization within the renal medulla in this study. By contrast to the findings in the F344/N rat, there was evidence (parathyroid gland hyperplasia, fibrous osteodystrophy, and glandular stomach mineralization) that chronic progressive nephropathy was more severe after 2 years in Wistar rats receiving 100 and 200 ppm, although there was no evidence of hyaline droplet nephropathy in male Wistar rats in the 13-week study. All of these considerations combined suggest that the neoplastic response to pyridine in the male F344/N rat kidney was not attributable to α 2u-globulin.

There was no evidence for a carcinogenic effect in the kidney of Wistar rats. The same diagnostic criteria and terminology were used in evaluating lesions in the kidney of both strains of rats. The severity of spontaneous nephropathy in control Wistar rats was moderate, whereas that in control male F344/N rats was mild. The results of these studies suggest that the male Wistar rat is not as susceptible as the male F344/N rat to the formation of kidney neoplasms from pyridine exposure. The NTP has not compared the susceptibility of male F344/N rats and male Wistar rats to other kidney carcinogens.

Liver: Liver lesions in F344/N rats were characterized by centrilobular cytomegaly, degeneration, and necrosis; cytoplasmic vacuolization; foci of cellular alteration; fibrosis; and pigmentation in Kupffer's cells and macrophages. Bile duct hyperplasia was observed in all exposed groups of males and females and the incidences were significantly increased in exposed females compared to controls. Periportal fibrosis was a prominent lesion in 400 ppm males. There were no statistically significant increases in the incidences of hepatocellular neoplasms in exposed F344/N or Wistar rats.

The same diagnostic criteria and terminology were applied to the liver lesions in both strains of rats. In general, except for the incidences of centrilobular cytomegaly, which was highest in 400 ppm females, periportal fibrosis, which was highest in 400 ppm male F344/N rats, and cytoplasmic vacuolization, which occurred in control and exposed Wistar rats, treatment-related nonneoplastic liver lesions occurred at higher incidences and with greater severities in Wistar rats than in male or female F344/N rats. These lesions, along with nephropathy, probably contributed to early deaths in Wistar rats. Incidences of fibrosis, extending from the liver capsule downwards into the parenchyma, were significantly increased relative to controls in 200 and 400 ppm Wistar rats but were increased less significantly in 400 ppm male F344/N rats and were not treatment related in females.

Exposure to pyridine was associated with progression of liver neoplasms from benign to malignant in male and female mice. Hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas represent a

biological and morphological continuum in progression of proliferative lesions. It is probable that hepatoblastomas do not represent further progression to a more malignant state but rather are composed of cells that are more primitive. Hepatoblastomas are considered to represent a phenotypic, and possibly genotypic, variant of a malignant liver neoplasm. Because the malignant potential of hepatocellular carcinomas and hepatoblastomas appear similar and hepatoblastomas are generally observed in the hepatocellular neoplasms (mostly carcinomas), it is appropriate to combine the incidences of hepatoblastomas with those of hepatocellular adenoma and carcinoma when interpreting the carcinogenic potential of a chemical. Hepatoblastomas, which are rare, are observed in relatively high numbers only after chemical administration (primarily in mice) and have previously been observed in NTP studies with primidone (NTP, 1999), oxazepam (NTP, 1993a), *o*-nitroanisole (NTP, 1993b), benzofuran (NTP, 1989), ethylene thiourea (NTP, 1992), 1-amino-2,4-dibromoanthraquinone (NTP, 1996), methylphenidate hydrochloride (NTP, 1995), and coumarin (NTP, 1993c).

Pyridine, like primidone (NTP, 1999), phenobarbital (McClain, 1990), and oxazepam (NTP, 1993a, 1998b), induces liver neoplasms in mice but not in rats, even though in rats these chemicals cause a spectrum of toxic liver lesions. The mouse, an animal with a high background rate of liver neoplasms, seems to be particularly sensitive to subsequent development of malignant liver neoplasms after chemical exposure (Drinkwater *et al.*, 1990; Drinkwater, 1994; Bennett *et al.*, 1995; Lee *et al.*, 1995). While there are no studies of the relationship between pyridine exposure and cancer incidence, it is of interest that use of primidone and phenobarbital to treat epilepsy in human (Olsen *et al.*, 1995).

Testis: In the Wistar rat at 2 years, the incidence of interstitial cell adenoma of the testis was increased in the 400 ppm group relative to controls. There was no corresponding increase in interstitial cell hyperplasia. The NTP does not have a historical database for neoplasms in Wistar rats. In one study analyzing neoplasm rates in 1,370 control Wistar rats (from Charles River Laboratories, Kingston, NY, or Hilltop Laboratory

Animals, Scottdale, PA, from 1980 to 1990) a control rate of 3.9% (range, 0%-22%) was reported for interstitial cell neoplasms of the testis in animals weighing between 556 and 717 g (Walsh and Poteracki, 1994). The rate for interstitial cell adenomas in Wistar rats exposed to 400 ppm pyridine was only marginally outside this historical range, and incidences of this neoplasm were not increased relative to controls in the 100 or 200 ppm groups. This was considered to be equivocal evidence for a carcinogenic effect. The mean body weights of the control male Wistar rats in this study were somewhat higher during the second year of the study (reaching a high of 803 g at week 73). Increased body weights have been associated with higher neoplasm rates at some sites in rodents, and this difference, combined with other differences in animal husbandry condition and time of study, may be a factor in the incidences of interstitial cell neoplasms observed in the present study. The spontaneous rate for interstitial cell neoplasms of the testis in F344/N rats is high (about 90%) and often precludes the conclusion of a carcinogenic effect at this site.

Mononuclear Cell Leukemia: Mononuclear cell leukemia is a common neoplasm in F344/N rats. The Wistar rat was added to these studies because it has a low background incidence of mononuclear cell leukemia in comparison to the male F344/N rat, and there was a suggestion from a study by Dieter *et al.* (1989) that pyridine may cause leukemia. However, in these studies, pyridine did not appear to affect the rate for leukemia in male rats. Incidences of mononuclear cell leukemia were increased relative to controls in 200 and 400 ppm F344/N female rats. These incidences were at or just outside the historical control range for this neoplasm, and because there was no supportive evidence for an increase in mononuclear cell leukemia in male rats compared with the incidences of mononuclear cell leukemia in control animals in a concurrent drinking water study at the same laboratory (19/50; NTP, 1998a), the rate observed in the 400 ppm group in this study does not seem to be significant.

Pyridine is metabolized primarily by N-methylation and/or aromatic hydroxylation. Metabolites identified include N-methylpyridinium, 3-hydroxy pyridine, and

N-methyl pyridinium hydroxide. Pyridine is metabolized by cytochromes P2E1 and P4B (CYP2E1 and CYP4B) (Nikula *et al.*, 1995) and enhances the expression of several forms of P₄₅₀, including CYP2E1, CYP1A1/1A2, and CYP2B1/2B2 in both hepatic and renal tissues (tissues from rat used as the model system) (Kim and Novak, 1990; Kim *et al.*, 1991a; Kim *et al.*, 1993).

Some studies suggest that the induction of cytochrome P₄₅₀2B enzymes are associated with mouse liver neoplasm formation (Lubet *et al.*, 1989; Rice *et al.*, 1994). Pyridine-induced liver neoplasms from control, 500 ppm male, and 1,000 ppm female mice showed no staining with p53 antibody, a marker that correlates with p53 gene alterations. Chemicals such as phenobarbital, which induces cytochrome P₄₅₀s in the rodent liver, induce a wide variety of enzyme systems (referred to as pleiotropic response), and it is likely that several effects of the chemical play a role in its liver neoplasm-promoting ability (McClain, 1990). Another nonmutagenic mouse liver carcinogen, methylphenidate, also showed no evidence for p53 protein accumulation in methylphenidate-induced liver neoplasms in the B6C3F₁ mouse and similar to pyridine was negative in the p53 (+/-) transgenic mouse model (Tennant *et al.*, 1995, 1999). Tennant *et al.* (1999) also reported that pyridine failed to induce a carcinogenic response in 6 month studies with the TgAC mouse, but Bucher (1998) pointed out that neither the TgAC nor the p53 (+/-) transgenic mouse assays appear responsive to chemicals that induce mouse liver neoplasms in standard 2-year assays.

There is a developing field of study regarding specific genetic changes in mouse and human liver neoplasms. In one series of human hepatoblastomas, p53 alterations were not seen in hepatoblastomas of fetal or mesenchymal origin but did occur in hepatoblastomas classified as small cell (Ruck *et al.*, 1994). Other studies also report a low frequency of p53 mutations in hepatoblastomas (Kar *et al.*, 1993; Kennedy *et al.*,

1994). In contrast, in a study of hepatoblastomas in Japanese patients, p53 mutations were found in nine of 10 cases (Oda *et al.*, 1995). Overexpression of p53 is a rare event in Caucasian patients with hepatocellular carcinoma (Laurent-Puig *et al.*, 1992).

Accumulation of p53 protein has been associated with liver neoplasms caused by viral hepatitis (42%) (Ojanguren *et al.*, 1995; Greenblatt *et al.*, 1997) and in aflatoxin hepatocarcinogenesis (Shen and Ong, 1996). Three studies of liver neoplasms in mice suggest that the p53 gene plays a minimal role in the development of these neoplasms (Kress *et al.*, 1992; Chen *et al.*, 1993; Calvert *et al.*, 1995). Mutations of the neoplasm suppressor gene p53 have been found in hepatocellular carcinomas from patients in many countries (e.g., Japan and Asian countries) where there may be an association between neoplasms and virus infection or aflatoxin exposure. In the United States, p53 mutations are usually not found in hepatocellular carcinomas (Kazachkov *et al.*, 1996), and the etiology of the liver cancer is not known.

Pyridine is negative in most studies for genotoxicity. Pyridine was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes. Further, no significant increase in mutant frequencies was observed in L5178Y mouse lymphoma cells, tested with and without S9 metabolic activation. In cytogenetic tests with cultured Chinese hamster ovary cells, pyridine did not induce sister chromatid exchanges or chromosomal aberrations, with or without S9. Results were positive for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster* following injection of pyridine but were negative by the same route of administration for induction of reciprocal translocations in germ cells of *D. melanogaster*. No induction of chromosomal aberrations and no increase in the frequency of micronucleated polychromatic erythrocytes was noted in mouse bone marrow cells after intraperitoneal injection of pyridine.

CONCLUSIONS

Under the conditions of these 2-year drinking water studies, there was *some evidence of carcinogenic activity** of pyridine in male F344/N rats based on increased incidences of renal tubule neoplasms. There was *equivocal evidence of carcinogenic activity* of pyridine in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was *equivocal evidence of carcinogenic activity* in male Wistar rats based on an increased incidence of interstitial cell adenoma of the testis. There was *clear evidence of carcinogenic activity* of pyridine in male and female B6C3F₁ mice based on increased incidences of malignant hepatocellular neoplasms.

In F344/N rats, exposure to pyridine resulted in increased incidences of centrilobular cytomegaly and degeneration, cytoplasmic vacuolization, and pigmentation in the liver of males and females; periportal fibrosis, fibrosis, and centrilobular necrosis in the liver of males; and bile duct hyperplasia in females. In male Wistar rats, pyridine exposure resulted in increased incidences of centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation in the liver, and secondary to kidney disease, mineralization in the glandular stomach and parathyroid gland hyperplasia.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 15.

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APPENDIX A

SUMMARY OF LESIONS IN MALE F344/N RATS IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

| | | |
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TABLE A1
Summary of the Incidence of Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine^a

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|-------------------------------------|----------|---------|----------|----------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 11 | 13 | 15 | 10 |
| Natural deaths | 14 | 17 | 10 | 24 |
| Survivors | | | | |
| Terminal sacrifice | 25 | 20 | 25 | 16 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| Alimentary System | | | | |
| Intestine large, colon | (50) | (48) | (50) | (49) |
| Lipoma | | | 1 (2%) | |
| Intestine large, cecum | (49) | (47) | (50) | (49) |
| Lipoma | | | 1 (2%) | |
| Intestine small, duodenum | (50) | (47) | (50) | (48) |
| Intestine small, jejunum | (50) | (47) | (50) | (47) |
| Carcinoma | 1 (2%) | | | |
| Intestine small, ileum | (50) | (47) | (50) | (47) |
| Liver | (50) | (49) | (50) | (50) |
| Cholangiocarcinoma | | | | 1 (2%) |
| Hepatocellular carcinoma | | | 1 (2%) | |
| Hepatocellular adenoma | 1 (2%) | 1 (2%) | | 2 (4%) |
| Hepatocellular adenoma, multiple | | | | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | | | |
| Mesentery | (11) | (14) | (7) | (8) |
| Schwannoma benign | 1 (9%) | | | |
| Oral mucosa | (1) | | (2) | |
| Pharyngeal, squamous cell papilloma | 1 (100%) | | 1 (50%) | |
| Pancreas | (50) | (48) | (50) | (49) |
| Acinus, adenoma | 2 (4%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Salivary glands | (50) | (50) | (50) | (50) |
| Stomach, forestomach | (50) | (49) | (50) | (49) |
| Squamous cell papilloma | | | 1 (2%) | |
| Stomach, glandular | (50) | (49) | (50) | (49) |
| Tongue | | | | (1) |
| Squamous cell papilloma | | | | 1 (100%) |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Endocrine System | | | | |
| Adrenal cortex | (50) | (49) | (50) | (50) |
| Carcinoma | | 1 (2%) | | |
| Adrenal medulla | (50) | (49) | (50) | (49) |
| Pheochromocytoma complex | | | | 1 (2%) |
| Pheochromocytoma benign | 11 (22%) | 2 (4%) | 14 (28%) | 4 (8%) |
| Bilateral, pheochromocytoma benign | 6 (12%) | 1 (2%) | | |
| Islets, pancreatic | (50) | (48) | (50) | (49) |
| Adenoma | 4 (8%) | 2 (4%) | 1 (2%) | |
| Parathyroid gland | (50) | (50) | (50) | (48) |

TABLE A1

Summary of the Incidence of Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---------------------------------------|----------|----------|----------|----------|
| Endocrine System (continued) | | | | |
| Pituitary gland | (50) | (50) | (50) | (50) |
| Pars distalis, adenoma | 16 (32%) | 13 (26%) | 12 (24%) | 11 (22%) |
| Pars intermedia, adenoma | 1 (2%) | | | |
| Thyroid gland | (50) | (50) | (50) | (49) |
| Bilateral, C-cell, adenoma | | 1 (2%) | | |
| C-cell, adenoma | 2 (4%) | | 3 (6%) | 2 (4%) |
| C-cell, carcinoma | | 1 (2%) | | |
| Follicular cell, adenoma | | 2 (4%) | | |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Epididymis | (49) | (49) | (49) | (48) |
| Preputial gland | (50) | (47) | (49) | (48) |
| Adenoma | 3 (6%) | | 7 (14%) | 2 (4%) |
| Carcinoma | 5 (10%) | 2 (4%) | | 1 (2%) |
| Prostate | (50) | (48) | (50) | (49) |
| Seminal vesicle | (50) | (47) | (50) | (48) |
| Testes | (49) | (49) | (49) | (48) |
| Bilateral, interstitial cell, adenoma | 33 (67%) | 35 (71%) | 37 (76%) | 40 (83%) |
| Interstitial cell, adenoma | 9 (18%) | 8 (16%) | 6 (12%) | 3 (6%) |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | 1 (2%) | | | |
| Melanoma malignant, metastatic, skin | | | 1 (2%) | |
| Lymph node | (20) | (25) | (20) | (23) |
| Lymph node, mandibular | (50) | (50) | (50) | (50) |
| Lymph node, mesenteric | (50) | (47) | (50) | (48) |
| Spleen | (49) | (48) | (50) | (49) |
| Thymus | (50) | (49) | (48) | (50) |
| Thymoma benign | | | | 1 (2%) |
| Integumentary System | | | | |
| Mammary gland | (49) | (48) | (50) | (49) |
| Carcinoma | | 1 (2%) | | |
| Fibroadenoma | 4 (8%) | 3 (6%) | 6 (12%) | 4 (8%) |
| Skin | (50) | (50) | (50) | (50) |
| Basal cell adenoma | | | | 1 (2%) |
| Keratoacanthoma | 6 (12%) | 4 (8%) | 1 (2%) | 5 (10%) |
| Keratoacanthoma, multiple | | | 1 (2%) | |
| Squamous cell papilloma | 4 (8%) | 1 (2%) | 1 (2%) | |
| Trichoepithelioma | | 1 (2%) | | 1 (2%) |
| Pinna, melanoma malignant | | | 1 (2%) | 2 (4%) |
| Subcutaneous tissue, fibroma | 4 (8%) | 2 (4%) | 4 (8%) | |
| Subcutaneous tissue, lipoma | 1 (2%) | | 1 (2%) | |
| Musculoskeletal System | | | | |
| Skeletal muscle | | (1) | | |

TABLE A1
Summary of the Incidence of Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|----------|----------|
| Nervous System | | | | |
| Brain | (50) | (50) | (48) | (50) |
| Oligodendroglioma malignant | | 1 (2%) | | |
| Spinal cord | (1) | | | |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | 1 (2%) | | | 4 (8%) |
| Alveolar/bronchiolar carcinoma | | | 2 (4%) | |
| Carcinoma, metastatic, mammary gland | | 1 (2%) | | |
| Carcinoma, metastatic, Zymbal's gland | | 1 (2%) | | |
| Melanoma malignant, metastatic, skin | | | 1 (2%) | |
| Osteosarcoma, metastatic, nose | 1 (2%) | | | |
| Nose | (50) | (50) | (49) | (50) |
| Osteosarcoma | 1 (2%) | | | |
| Respiratory epithelium, squamous cell carcinoma | | 1 (2%) | | |
| Trachea | (50) | (50) | (50) | (50) |
| Special Senses System | | | | |
| Zymbal's gland | (1) | (1) | (1) | (1) |
| Carcinoma | 1 (100%) | 1 (100%) | 1 (100%) | 1 (100%) |
| Urinary System | | | | |
| Kidney | (50) | (48) | (50) | (49) |
| Mesenchymal tumor malignant | | 1 (2%) | | |
| Renal tubule, adenoma | 1 (2%) | | 1 (2%) | 4 (8%) |
| Renal tubule, adenoma, multiple | | | 1 (2%) | 2 (4%) |
| Renal tubule, carcinoma | | 1 (2%) | | |
| Urinary bladder | (50) | (47) | (50) | (49) |
| Systemic Lesions | | | | |
| Multiple organs ^b | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | 1 (2%) | | | |
| Leukemia mononuclear | 29 (58%) | 32 (64%) | 26 (52%) | 27 (54%) |
| Lymphoma malignant | | | | 1 (2%) |
| Mesothelioma benign | 1 (2%) | | 1 (2%) | |
| Mesothelioma malignant | 1 (2%) | 1 (2%) | | |
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^c | 49 | 49 | 49 | 49 |
| Total primary neoplasms | 151 | 120 | 133 | 123 |
| Total animals with benign neoplasms | 47 | 46 | 48 | 49 |
| Total benign neoplasms | 112 | 77 | 102 | 89 |
| Total animals with malignant neoplasms | 34 | 40 | 29 | 29 |
| Total malignant neoplasms | 39 | 43 | 31 | 34 |
| Total animals with metastatic neoplasms | 1 | 2 | 1 | |
| Total metastatic neoplasms | 1 | 2 | 2 | |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2

Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

| Number of Days on Study | 3 | 3 | 3 | 4 | 4 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 |
|-------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 8 | 8 | 3 | 7 | 7 | 7 | 7 | 9 | 0 | 0 | 2 | 4 | 4 | 5 | 6 | 6 | 9 | 9 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 9 | 8 | 8 | 4 | 3 | 1 | 4 | 9 | 5 | 2 | 4 | 5 | 0 | 4 | 6 | 7 | 7 | 2 | 5 | 1 | 5 | 8 | 8 | 9 | 9 | |
| Carcass ID Number | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2 | 1 | 3 | 4 | 2 | 4 | 4 | 1 | 1 | 1 | 0 | 3 | 0 | 3 | 4 | 1 | 4 | 0 | 0 | 2 | 4 | 0 | 1 | 0 | 1 | |
| | 5 | 2 | 4 | 5 | 3 | 1 | 8 | 5 | 1 | 0 | 7 | 6 | 4 | 8 | 3 | 9 | 4 | 2 | 1 | 2 | 9 | 5 | 6 | 3 | 3 | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Schwannoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pharyngeal, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Acinus, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pars intermedia, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Penis | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
|-------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--------------------|--|
| Number of Days on Study | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| Carcass ID Number | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Total | |
| | 0 | 0 | 0 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 5 | Tissues/ Tumors | |
| | 6 | 8 | 9 | 4 | 7 | 8 | 0 | 1 | 4 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 5 | 7 | 9 | 0 | 2 | 6 | 7 | 0 | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 | |
| Mesentery | + | | + | | | | | | + | | | | | | | | | | | | | | | | + | 11 | |
| Schwannoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Pharyngeal, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Acinus, adenoma | | | | | | | | | X | | | | | | | | | | | X | | | | | | 2 | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Tooth | | | | | + | | | + | | | | | | | | | | | | | | | | | | 2 | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Pheochromocytoma benign | | | | | | X | | | X | | | | | X | | | | X | | | X | X | X | | | 11 | |
| Bilateral, pheochromocytoma benign | | | | | | | | X | | | | | | | | X | X | X | | | | | | | | 6 | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Adenoma | | | | | | | | X | | | | | | | | | | | | | | | | | | 4 | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Pars distalis, adenoma | | | | X | X | | | X | X | X | | X | | | | X | X | | | | | X | | | | 16 | |
| Pars intermedia, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| C-cell, adenoma | | X | | | X | | | | | | | | | | | | | | | | | | | | | 2 | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Penis | | | | | | | | | | | + | | | | | | | | | | | | | | | 1 | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Adenoma | | | | | | | | | X | | | | | | | | X | | | | | | | | | 3 | |
| Carcinoma | | | | | | | | | | | | | | | X | | | | | X | | | X | X | | 5 | |

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 4 | 4 | 4 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | |
| Number of Days on Study | 4 | 5 | 6 | 3 | 5 | 9 | 0 | 0 | 0 | 1 | 2 | 2 | 2 | 4 | 4 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 8 | |
| | 4 | 5 | 6 | 8 | 3 | 8 | 4 | 4 | 7 | 8 | 0 | 5 | 8 | 1 | 2 | 4 | 5 | 5 | 6 | 6 | 6 | 7 | 3 | 7 | 2 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Carcass ID Number | 9 | 9 | 5 | 7 | 9 | 6 | 7 | 8 | 7 | 8 | 0 | 8 | 7 | 5 | 6 | 9 | 6 | 7 | 5 | 6 | 7 | 9 | 9 | 9 | 6 | |
| | 4 | 9 | 6 | 7 | 8 | 9 | 9 | 1 | 2 | 7 | 0 | 9 | 1 | 3 | 2 | 1 | 0 | 4 | 2 | 7 | 3 | 0 | 6 | 5 | 6 | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | M | + | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | + | + | | | + | | | | | + | | | | + | + | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Acinus, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | | | | X | | | X | | X | | X | X | X | | X | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | |
| Preputial gland | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Bilateral, interstitial cell, adenoma | X | | X | X | | X | X | X | X | | X | | X | X | | | X | | X | X | | | | | X | |
| Interstitial cell, adenoma | | X | | | | | | | | X | | | | | X | X | | | | | X | X | | | | |

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE A2

[illegible]

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | | |
| Number of Days on Study | 6 | 8 | 2 | 2 | 3 | 3 | 8 | 8 | 8 | 9 | 0 | 2 | 3 | 4 | 4 | 4 | 4 | 6 | 6 | 7 | 7 | 0 | 0 | 0 | 1 |
| | 9 | 6 | 5 | 9 | 4 | 8 | 0 | 5 | 9 | 6 | 9 | 7 | 2 | 0 | 4 | 8 | 8 | 2 | 9 | 3 | 9 | 0 | 0 | 8 | 9 |
| Carcass ID Number | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| | 1 | 3 | 1 | 4 | 2 | 4 | 1 | 3 | 0 | 0 | 4 | 5 | 4 | 3 | 0 | 3 | 3 | 2 | 2 | 4 | 1 | 1 | 2 | 1 | 3 |
| | 7 | 8 | 5 | 9 | 3 | 7 | 3 | 3 | 4 | 8 | 6 | 0 | 2 | 4 | 9 | 0 | 1 | 9 | 0 | 8 | 6 | 8 | 1 | 4 | 7 |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Lipoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Lipoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | + | | + | | | + | + | | | | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | + | | | | | |
| Pharyngeal, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Acinus, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Adrenal medulla | + | + | + | + | + | + | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Pheochromocytoma benign | | | | | | | | X | | | X | | | | | X | X | | X | X | | | | X | |
| Islets, pancreatic | + | + | + | + | + | + | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Pars distalis, adenoma | X | | X | | X | X | | | | | X | | | X | | | | | | | | X | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | |
| Adenoma | | | | | X | X | | | | X | | | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | |
| Bilateral, interstitial cell, adenoma | | | | | X | | | X | | X | | X | | | | X | X | X | X | X | X | X | X | X | |
| Interstitial cell, adenoma | | | | | | | X | X | | X | | X | | | X | | | | | | | | | | |

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

[illegible]

TABLE A2[illegible]

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----|--------------------------|
| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| Number of Days on Study | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| Carcass ID Number | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Total Tissues/ Tumors |
| | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | |
| | 1 | 2 | 3 | 5 | 6 | 7 | 0 | 1 | 2 | 9 | 2 | 4 | 5 | 6 | 7 | 8 | 2 | 5 | 6 | 9 | 0 | 1 | 3 | 4 | 5 | | |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Melanoma malignant, metastatic, skin | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 | |
| Lymph node | | | | | | | | | + | | | | | + | + | | | | | | + | | | | + | 20 | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Thymus | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | | 48 | |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Fibroadenoma | | | | | | | | | | | | | | X | | | | X | | | | | | X | | 6 | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Keratoacanthoma | | | | | | X | | | | | | | | | | | | | | | | | | | | 1 | |
| Keratoacanthoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 | |
| Pinna, melanoma malignant | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 | |
| Subcutaneous tissue, fibroma | | | | X | | | | | | | | | | | X | | | | | | | | | | | 4 | |
| Subcutaneous tissue, lipoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | 48 | |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | X | X | | | | | | | | | | | | | | 2 | |
| Melanoma malignant, metastatic, skin | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 | |
| Nose | + | + | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 | |
| Renal tubule, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Leukemia mononuclear | | | | | X | | X | X | | | | | X | | | X | X | X | | X | X | X | X | | | 26 | |
| Mesothelioma benign | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 | |

TABLE A2

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Number of Days on Study | 9 | 2 | 4 | 6 | 1 | 2 | 2 | 4 | 6 | 8 | 9 | 0 | 1 | 2 | 2 | 3 | 4 | 4 | 4 | 5 | 7 | 7 | 7 | 7 | 8 |
| | 4 | 8 | 4 | 5 | 5 | 0 | 3 | 3 | 2 | 4 | 8 | 1 | 6 | 2 | 7 | 4 | 4 | 7 | 7 | 1 | 0 | 2 | 5 | 6 | 1 |
| | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Carcass ID Number | 5 | 7 | 6 | 9 | 7 | 9 | 6 | 7 | 6 | 9 | 9 | 9 | 5 | 5 | 8 | 5 | 6 | 5 | 8 | 5 | 8 | 7 | 6 | 8 | 6 |
| | 5 | 7 | 3 | 9 | 4 | 8 | 5 | 0 | 2 | 2 | 5 | 1 | 2 | 4 | 7 | 1 | 9 | 3 | 3 | 6 | 0 | 1 | 6 | 8 | 0 |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cholangiocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | + | | | | | | + | | | + | + | | | + | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Acinus, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Pheochromocytoma complex | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | X | | | | | | X | | X | | X | | X | | X | X | | | | | | | |
| Thyroid gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | | | X | X | X | | X | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |
| Interstitial cell, adenoma | | | | | | | X | | | | | | | | X | | X | | | | | | | | |

TABLE A2[illegible]

TABLE A3

Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|-------------|----------------|-------------|-------------|
| Adrenal Medulla: Benign Pheochromocytoma | | | | |
| Overall rate ^a | 17/50 (34%) | 3/49 (6%) | 14/50 (28%) | 4/49 (8%) |
| Adjusted rate ^b | 40.4% | 7.5% | 32.8% | 10.6% |
| Terminal rate ^c | 11/25 (44%) | 1/20 (5%) | 7/25 (28%) | 3/16 (19%) |
| First incidence (days) | 571 | 628 | 585 | 675 |
| Poly-3 test ^d | P=0.014N | P<0.001N | P=0.306N | P=0.002N |
| Adrenal Medulla: Benign or Complex Pheochromocytoma | | | | |
| Overall rate | 17/50 (34%) | 3/49 (6%) | 14/50 (28%) | 5/49 (10%) |
| Adjusted rate | 40.4% | 7.5% | 32.8% | 13.3% |
| Terminal rate | 11/25 (44%) | 1/20 (5%) | 7/25 (28%) | 4/16 (25%) |
| First incidence (days) | 571 | 628 | 585 | 675 |
| Poly-3 test | P=0.030N | P<0.001N | P=0.306N | P=0.005N |
| Kidney (Renal Tubule): Adenoma (Single Sections) | | | | |
| Overall rate | 1/50 (2%) | 0/48 (0%) | 2/50 (4%) | 6/49 (12%) |
| Adjusted rate | 2.4% | 0.0% | 4.9% | 15.9% |
| Terminal rate | 1/25 (4%) | 0/20 (0%) | 1/25 (4%) | 2/16 (13%) |
| First incidence (days) | 722 (T) | — ^e | 708 | 644 |
| Poly-3 test | P=0.003 | P=0.510N | P=0.498 | P=0.042 |
| Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections) | | | | |
| Overall rate | 1/50 (2%) | 1/48 (2%) | 2/50 (4%) | 6/49 (12%) |
| Adjusted rate | 2.4% | 2.6% | 4.9% | 15.9% |
| Terminal rate | 1/25 (4%) | 1/20 (5%) | 1/25 (4%) | 2/16 (13%) |
| First incidence (days) | 722 (T) | 722 (T) | 708 | 644 |
| Poly-3 test | P=0.008 | P=0.750 | P=0.498 | P=0.042 |
| Kidney (Renal Tubule): Adenoma (Single and Step Sections) | | | | |
| Overall rate | 2/50 (4%) | 3/48 (6%) | 6/50 (12%) | 10/49 (20%) |
| Adjusted rate | 4.9% | 7.6% | 14.5% | 26.3% |
| Terminal rate | 2/25 (8%) | 2/20 (10%) | 3/25 (12%) | 5/16 (31%) |
| First incidence (days) | 722 (T) | 673 | 627 | 644 |
| Poly-3 test | P=0.002 | P=0.480 | P=0.133 | P=0.008 |
| Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections) | | | | |
| Overall rate | 2/50 (4%) | 4/48 (8%) | 6/50 (12%) | 10/49 (20%) |
| Adjusted rate | 4.9% | 10.2% | 14.5% | 26.3% |
| Terminal rate | 2/25 (8%) | 3/20 (15%) | 3/25 (12%) | 5/16 (31%) |
| First incidence (days) | 722 (T) | 673 | 627 | 644 |
| Poly-3 test | P=0.003 | P=0.316 | P=0.133 | P=0.008 |
| Liver: Hepatocellular Adenoma | | | | |
| Overall rate | 1/50 (2%) | 1/49 (2%) | 0/50 (0%) | 3/50 (6%) |
| Adjusted rate | 2.4% | 2.5% | 0.0% | 7.8% |
| Terminal rate | 0/25 (0%) | 1/20 (5%) | 0/25 (0%) | 1/16 (6%) |
| First incidence (days) | 718 | 722 (T) | — | 622 |
| Poly-3 test | P=0.153 | P=0.754 | P=0.501N | P=0.283 |
| Liver: Hepatocellular Adenoma or Carcinoma | | | | |
| Overall rate | 1/50 (2%) | 1/49 (2%) | 1/50 (2%) | 3/50 (6%) |
| Adjusted rate | 2.4% | 2.5% | 2.4% | 7.8% |
| Terminal rate | 0/25 (0%) | 1/20 (5%) | 1/25 (4%) | 1/16 (6%) |
| First incidence (days) | 718 | 722 (T) | 722 (T) | 622 |
| Poly-3 test | P=0.153 | P=0.754 | P=0.760 | P=0.283 |

TABLE A3

Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|-------------|-------------|-------------|-------------|
| Lung: Alveolar/bronchiolar Adenoma | | | | |
| Overall rate | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 4/50 (8%) |
| Adjusted rate | 2.4% | 0.0% | 0.0% | 10.4% |
| Terminal rate | 1/25 (4%) | 0/20 (0%) | 0/25 (0%) | 3/16 (19%) |
| First incidence (days) | 722 (T) | — | — | 697 |
| Poly-3 test | P=0.024 | P=0.503N | P=0.501N | P=0.157 |
| Lung: Alveolar/bronchiolar Adenoma or Carcinoma | | | | |
| Overall rate | 1/50 (2%) | 0/50 (0%) | 2/50 (4%) | 4/50 (8%) |
| Adjusted rate | 2.4% | 0.0% | 4.9% | 10.4% |
| Terminal rate | 1/25 (4%) | 0/20 (0%) | 2/25 (8%) | 3/16 (19%) |
| First incidence (days) | 722 (T) | — | 722 (T) | 697 |
| Poly-3 test | P=0.033 | P=0.503N | P=0.498 | P=0.157 |
| Mammary Gland: Fibroadenoma | | | | |
| Overall rate | 4/50 (8%) | 3/50 (6%) | 6/50 (12%) | 4/50 (8%) |
| Adjusted rate | 9.7% | 7.4% | 14.4% | 10.4% |
| Terminal rate | 3/25 (12%) | 2/20 (10%) | 3/25 (12%) | 1/16 (6%) |
| First incidence (days) | 718 | 708 | 538 | 681 |
| Poly-3 test | P=0.439 | P=0.507N | P=0.378 | P=0.609 |
| Mammary Gland: Fibroadenoma or Carcinoma | | | | |
| Overall rate | 4/50 (8%) | 4/50 (8%) | 6/50 (12%) | 4/50 (8%) |
| Adjusted rate | 9.7% | 9.9% | 14.4% | 10.4% |
| Terminal rate | 3/25 (12%) | 3/20 (15%) | 3/25 (12%) | 1/16 (6%) |
| First incidence (days) | 718 | 708 | 538 | 681 |
| Poly-3 test | P=0.487 | P=0.637 | P=0.378 | P=0.609 |
| Pancreatic Islets: Adenoma | | | | |
| Overall rate | 4/50 (8%) | 2/48 (4%) | 1/50 (2%) | 0/49 (0%) |
| Adjusted rate | 9.6% | 5.1% | 2.4% | 0.0% |
| Terminal rate | 1/25 (4%) | 2/20 (10%) | 1/25 (4%) | 0/16 (0%) |
| First incidence (days) | 625 | 722 (T) | 722 (T) | — |
| Poly-3 test | P=0.033N | P=0.366N | P=0.184N | P=0.075N |
| Pituitary Gland (Pars Distalis): Adenoma | | | | |
| Overall rate | 16/50 (32%) | 13/50 (26%) | 12/50 (24%) | 11/50 (22%) |
| Adjusted rate | 36.9% | 31.0% | 27.0% | 26.6% |
| Terminal rate | 9/25 (36%) | 7/20 (35%) | 5/25 (20%) | 3/16 (19%) |
| First incidence (days) | 434 | 628 | 269 | 428 |
| Poly-3 test | P=0.177N | P=0.365N | P=0.221N | P=0.215N |
| Preputial Gland: Adenoma | | | | |
| Overall rate | 3/50 (6%) | 0/47 (0%) | 7/49 (14%) | 2/48 (4%) |
| Adjusted rate | 7.2% | 0.0% | 16.7% | 5.4% |
| Terminal rate | 2/25 (8%) | 0/19 (0%) | 4/25 (16%) | 2/16 (13%) |
| First incidence (days) | 604 | — | 529 | 722 (T) |
| Poly-3 test | P=0.427 | P=0.134N | P=0.158 | P=0.556N |
| Preputial Gland: Carcinoma | | | | |
| Overall rate | 5/50 (10%) | 2/47 (4%) | 0/49 (0%) | 1/48 (2%) |
| Adjusted rate | 11.9% | 5.3% | 0.0% | 2.7% |
| Terminal rate | 4/25 (16%) | 2/19 (11%) | 0/25 (0%) | 1/16 (6%) |
| First incidence (days) | 388 | 722 (T) | — | 722 (T) |
| Poly-3 test | P=0.046N | P=0.255N | P=0.034N | P=0.133N |

TABLE A3

Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|-------------|-------------|-------------|--------------|
| Preputial Gland: Adenoma or Carcinoma | | | | |
| Overall rate | 8/50 (16%) | 2/47 (4%) | 7/49 (14%) | 3/48 (6%) |
| Adjusted rate | 18.9% | 5.3% | 16.7% | 8.2% |
| Terminal rate | 6/25 (24%) | 2/19 (11%) | 4/25 (16%) | 3/16 (19%) |
| First incidence (days) | 388 | 722 (T) | 529 | 722 (T) |
| Poly-3 test | P=0.212N | P=0.063N | P=0.511N | P=0.146N |
| Skin: Squamous Cell Papilloma | | | | |
| Overall rate | 4/50 (8%) | 1/50 (2%) | 1/50 (2%) | 0/50 (0%) |
| Adjusted rate | 9.7% | 2.5% | 2.4% | 0.0% |
| Terminal rate | 4/25 (16%) | 1/20 (5%) | 1/25 (4%) | 0/16 (0%) |
| First incidence (days) | 722 (T) | 722 (T) | 722 (T) | — |
| Poly-3 test | P=0.035N | P=0.181N | P=0.179N | P=0.069N |
| Skin: Keratoacanthoma | | | | |
| Overall rate | 6/50 (12%) | 4/50 (8%) | 2/50 (4%) | 5/50 (10%) |
| Adjusted rate | 14.5% | 9.8% | 4.9% | 12.9% |
| Terminal rate | 5/25 (20%) | 2/20 (10%) | 1/25 (4%) | 1/16 (6%) |
| First incidence (days) | 656 | 673 | 708 | 670 |
| Poly-3 test | P=0.474N | P=0.378N | P=0.134N | P=0.548N |
| Skin: Squamous Cell Papilloma or Keratoacanthoma | | | | |
| Overall rate | 8/50 (16%) | 5/50 (10%) | 3/50 (6%) | 5/50 (10%) |
| Adjusted rate | 19.3% | 12.3% | 7.3% | 12.9% |
| Terminal rate | 7/25 (28%) | 3/20 (15%) | 2/25 (8%) | 1/16 (6%) |
| First incidence (days) | 656 | 673 | 708 | 670 |
| Poly-3 test | P=0.250N | P=0.282N | P=0.099N | P=0.318N |
| Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma | | | | |
| Overall rate | 8/50 (16%) | 6/50 (12%) | 3/50 (6%) | 7/50 (14%) |
| Adjusted rate | 19.3% | 14.7% | 7.3% | 18.1% |
| Terminal rate | 7/25 (28%) | 4/20 (20%) | 2/25 (8%) | 2/16 (13%) |
| First incidence (days) | 656 | 673 | 708 | 670 |
| Poly-3 test | P=0.474N | P=0.396N | P=0.099N | P=0.556N |
| Skin (Subcutaneous Tissue): Fibroma | | | | |
| Overall rate | 4/50 (8%) | 2/50 (4%) | 4/50 (8%) | 0/50 (0%) |
| Adjusted rate | 9.6% | 4.8% | 9.6% | 0.0% |
| Terminal rate | 2/25 (8%) | 0/20 (0%) | 2/25 (8%) | 0/16 (0%) |
| First incidence (days) | 625 | 553 | 580 | — |
| Poly-3 test | P=0.092N | P=0.341N | P=0.642 | P=0.071N |
| Testes: Adenoma | | | | |
| Overall rate | 42/49 (86%) | 43/49 (88%) | 43/49 (88%) | 43/48 (90%) |
| Adjusted rate | 93.0% | 90.2% | 93.2% | 95.6% |
| Terminal rate | 23/25 (92%) | 18/20 (90%) | 24/25 (96%) | 16/16 (100%) |
| First incidence (days) | 473 | 444 | 529 | 444 |
| Poly-3 test | P=0.275 | P=0.450N | P=0.662 | P=0.464 |
| Thyroid Gland (C-cell): Adenoma | | | | |
| Overall rate | 2/50 (4%) | 1/50 (2%) | 3/50 (6%) | 2/49 (4%) |
| Adjusted rate | 4.9% | 2.5% | 7.3% | 5.2% |
| Terminal rate | 2/25 (8%) | 1/20 (5%) | 3/25 (12%) | 2/16 (13%) |
| First incidence (days) | 722 (T) | 722 (T) | 722 (T) | 722 (T) |
| Poly-3 test | P=0.466 | P=0.505N | P=0.497 | P=0.668 |

TABLE A3
Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|--------------|--------------|--------------|--------------|
| Thyroid Gland (C-cell): Adenoma or Carcinoma | | | | |
| Overall rate | 2/50 (4%) | 2/50 (4%) | 3/50 (6%) | 2/49 (4%) |
| Adjusted rate | 4.9% | 4.9% | 7.3% | 5.2% |
| Terminal rate | 2/25 (8%) | 1/20 (5%) | 3/25 (12%) | 2/16 (13%) |
| First incidence (days) | 722 (T) | 666 | 722 (T) | 722 (T) |
| Poly-3 test | P=0.531 | P=0.691 | P=0.497 | P=0.668 |
| All Organs: Mononuclear Cell Leukemia | | | | |
| Overall rate | 29/50 (58%) | 32/50 (64%) | 26/50 (52%) | 27/50 (54%) |
| Adjusted rate | 62.7% | 67.8% | 57.4% | 59.7% |
| Terminal rate | 13/25 (52%) | 11/20 (55%) | 12/25 (48%) | 7/16 (44%) |
| First incidence (days) | 309 | 466 | 529 | 444 |
| Poly-3 test | P=0.317N | P=0.378 | P=0.381N | P=0.468N |
| All Organs: Benign Neoplasms | | | | |
| Overall rate | 47/50 (94%) | 46/50 (92%) | 48/50 (96%) | 49/50 (98%) |
| Adjusted rate | 99.2% | 93.4% | 98.0% | 100.0% |
| Terminal rate | 25/25 (100%) | 19/20 (95%) | 25/25 (100%) | 16/16 (100%) |
| First incidence (days) | 434 | 444 | 269 | 428 |
| Poly-3 test | P=0.228 | P=0.136N | P=0.712N | P=0.996 |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 34/50 (68%) | 40/50 (80%) | 29/50 (58%) | 29/50 (58%) |
| Adjusted rate | 71.8% | 81.5% | 63.1% | 63.9% |
| Terminal rate | 16/25 (64%) | 14/20 (70%) | 14/25 (56%) | 8/16 (50%) |
| First incidence (days) | 309 | 444 | 486 | 444 |
| Poly-3 test | P=0.091N | P=0.182 | P=0.243N | P=0.270N |
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 49/50 (98%) | 49/50 (98%) | 49/50 (98%) | 49/50 (98%) |
| Adjusted rate | 99.7% | 98.3% | 98.6% | 100.0% |
| Terminal rate | 25/25 (100%) | 20/20 (100%) | 25/25 (100%) | 16/16 (100%) |
| First incidence (days) | 309 | 444 | 269 | 428 |
| Poly-3 test | P=0.580 | P=0.656N | P=0.760N | P=1.000 |

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, lung, pancreatic islets, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE A4
Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats^a

| | Incidence in Controls | | |
|-------------------------------------|-----------------------|-----------|----------------------|
| | Adenoma | Carcinoma | Adenoma or Carcinoma |
| Overall Historical Incidence | | | |
| Total | 1/327 (0.3%) | 0/327 | 1/327 (0.3%) |
| Standard deviation | 0.8% | | 0.8% |
| Range | 0%-2% | | 0%-2% |

^a Data as of 1 August 1997

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine^a

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|----------------------------------|----------|----------|----------|----------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 11 | 13 | 15 | 10 |
| Natural deaths | 14 | 17 | 10 | 24 |
| Survivors | | | | |
| Terminal sacrifice | 25 | 20 | 25 | 16 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| Alimentary System | | | | |
| Intestine large, colon | (50) | (48) | (50) | (49) |
| Hyperplasia, lymphoid | | | 1 (2%) | |
| Inflammation, acute | | | 1 (2%) | |
| Inflammation, chronic | | | 1 (2%) | |
| Parasite metazoan | 4 (8%) | 4 (8%) | 3 (6%) | 2 (4%) |
| Intestine large, rectum | (50) | (48) | (50) | (49) |
| Edema | | 1 (2%) | | |
| Parasite metazoan | 4 (8%) | 2 (4%) | | 1 (2%) |
| Intestine large, cecum | (49) | (47) | (50) | (49) |
| Edema | | 1 (2%) | | |
| Hyperplasia, lymphoid | | 1 (2%) | | |
| Inflammation, acute | 1 (2%) | | 1 (2%) | 1 (2%) |
| Inflammation, chronic active | | 1 (2%) | | |
| Parasite metazoan | | | 1 (2%) | 1 (2%) |
| Ulcer | 1 (2%) | | | |
| Intestine small, duodenum | (50) | (47) | (50) | (48) |
| Ectopic pancreas | | | 1 (2%) | |
| Intestine small, jejunum | (50) | (47) | (50) | (47) |
| Congestion | | 1 (2%) | | |
| Intestine small, ileum | (50) | (47) | (50) | (47) |
| Fibrosis | 1 (2%) | | | |
| Hyperplasia, lymphoid | 6 (12%) | 9 (19%) | 3 (6%) | 4 (9%) |
| Liver | (50) | (49) | (50) | (50) |
| Angiectasis | | 1 (2%) | 1 (2%) | 1 (2%) |
| Basophilic focus | 12 (24%) | 5 (10%) | | 1 (2%) |
| Clear cell focus | 7 (14%) | 1 (2%) | 7 (14%) | 4 (8%) |
| Congestion | 1 (2%) | | | |
| Degeneration, cystic | 4 (8%) | 12 (24%) | 11 (22%) | 3 (6%) |
| Developmental malformation | | | 1 (2%) | 1 (2%) |
| Eosinophilic focus | 14 (28%) | 23 (47%) | 23 (46%) | 13 (26%) |
| Fibrosis | 1 (2%) | 1 (2%) | 1 (2%) | 10 (20%) |
| Hematopoietic cell proliferation | 2 (4%) | 1 (2%) | | |
| Hepatodiaphragmatic nodule | 3 (6%) | 1 (2%) | | |
| Mitotic alteration | | | | 2 (4%) |
| Mixed cell focus | 2 (4%) | 1 (2%) | 3 (6%) | 1 (2%) |
| Necrosis | 2 (4%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Pigmentation | 4 (8%) | 11 (22%) | 20 (40%) | 25 (50%) |
| Thrombosis | | | 1 (2%) | |
| Vacuolization cytoplasmic | 4 (8%) | 6 (12%) | 13 (26%) | 17 (34%) |
| Bile duct, hyperplasia | 46 (92%) | 43 (88%) | 44 (88%) | 49 (98%) |
| Centrilobular, cytomegaly | | 4 (8%) | 8 (16%) | 6 (12%) |
| Centrilobular, degeneration | 1 (2%) | 3 (6%) | 2 (4%) | 8 (16%) |
| Centrilobular, necrosis | | 3 (6%) | | 5 (10%) |
| Periportal, fibrosis | | | 2 (4%) | 29 (58%) |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|----------|----------|
| Alimentary System (continued) | | | | |
| Mesentery | (11) | (14) | (7) | (8) |
| Cyst | 1 (9%) | | | |
| Hemorrhage | | | 1 (14%) | |
| Inflammation, acute | | 1 (7%) | | |
| Fat, necrosis | 10 (91%) | 13 (93%) | 6 (86%) | 8 (100%) |
| Oral mucosa | (1) | | (2) | |
| Pharyngeal, hyperplasia | | | 1 (50%) | |
| Pancreas | (50) | (48) | (50) | (49) |
| Atrophy | 18 (36%) | 15 (31%) | 17 (34%) | 12 (24%) |
| Cytoplasmic alteration | 2 (4%) | | | |
| Hyperplasia | 2 (4%) | 4 (8%) | 2 (4%) | 3 (6%) |
| Inflammation, chronic | 1 (2%) | | 3 (6%) | |
| Acinus, hyperplasia | | 1 (2%) | | |
| Artery, inflammation, acute | 1 (2%) | | | |
| Salivary glands | (50) | (50) | (50) | (50) |
| Cellular alteration | | | | 1 (2%) |
| Inflammation, chronic active | | 1 (2%) | | |
| Stomach, forestomach | (50) | (49) | (50) | (49) |
| Hyperkeratosis | | | | 2 (4%) |
| Inflammation, acute | | 1 (2%) | | 1 (2%) |
| Inflammation, chronic active | 2 (4%) | | | 8 (16%) |
| Ulcer | 2 (4%) | 10 (20%) | 3 (6%) | 4 (8%) |
| Epithelium, hyperplasia, squamous | 1 (2%) | 7 (14%) | 7 (14%) | 11 (22%) |
| Stomach, glandular | (50) | (49) | (50) | (49) |
| Erosion | 15 (30%) | 17 (35%) | 12 (24%) | 12 (24%) |
| Inflammation, acute | | | | 1 (2%) |
| Inflammation, chronic | 1 (2%) | 1 (2%) | | |
| Inflammation, chronic active | | | 1 (2%) | 1 (2%) |
| Mineralization | | 2 (4%) | 2 (4%) | 8 (16%) |
| Necrosis | | | | 1 (2%) |
| Ulcer | 2 (4%) | 5 (10%) | 1 (2%) | 1 (2%) |
| Tooth | (2) | (1) | (1) | |
| Dysplasia | | 1 (100%) | | |
| Inflammation, acute | 1 (50%) | | | |
| Inflammation, chronic active | 1 (50%) | | 1 (100%) | |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy | 45 (90%) | 43 (86%) | 43 (86%) | 46 (92%) |
| Mineralization | 1 (2%) | | 3 (6%) | 2 (4%) |
| Thrombosis | 2 (4%) | 6 (12%) | 3 (6%) | 4 (8%) |
| Coronary artery, inflammation, chronic active | | 1 (2%) | | |
| Endocrine System | | | | |
| Adrenal cortex | (50) | (49) | (50) | (50) |
| Accessory adrenal cortical nodule | 1 (2%) | | | 1 (2%) |
| Congestion | | | 1 (2%) | |
| Hyperplasia | 8 (16%) | 7 (14%) | 7 (14%) | 2 (4%) |
| Hypertrophy | 1 (2%) | | | 2 (4%) |
| Vacuolization cytoplasmic | 9 (18%) | 5 (10%) | 9 (18%) | 7 (14%) |
| Adrenal medulla | (50) | (49) | (50) | (49) |
| Hyperplasia | 17 (34%) | 22 (45%) | 19 (38%) | 15 (31%) |
| Bilateral, hyperplasia | 1 (2%) | 1 (2%) | | 1 (2%) |

TABLE A5

Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|----------|----------|
| Endocrine System (continued) | | | | |
| Islets, pancreatic | (50) | (48) | (50) | (49) |
| Hyperplasia | 5 (10%) | 2 (4%) | 1 (2%) | 1 (2%) |
| Parathyroid gland | (50) | (50) | (50) | (48) |
| Hyperplasia | | 1 (2%) | 3 (6%) | 3 (6%) |
| Pituitary gland | (50) | (50) | (50) | (50) |
| Pars distalis, angiectasis | | 2 (4%) | 2 (4%) | 2 (4%) |
| Pars distalis, cyst | 2 (4%) | 8 (16%) | 3 (6%) | 1 (2%) |
| Pars distalis, degeneration | | | | 1 (2%) |
| Pars distalis, ectasia | | 1 (2%) | | |
| Pars distalis, hemorrhage | 1 (2%) | | | |
| Pars distalis, hyperplasia | 22 (44%) | 16 (32%) | 18 (36%) | 12 (24%) |
| Pars distalis, thrombosis | | 1 (2%) | | |
| Thyroid gland | (50) | (50) | (50) | (49) |
| Pigmentation | | 1 (2%) | | |
| Ultimobranchial cyst | 1 (2%) | 1 (2%) | | 1 (2%) |
| C-cell, hyperplasia | 7 (14%) | 5 (10%) | 3 (6%) | 3 (6%) |
| Follicle, dilatation | 1 (2%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Follicular cell, hyperplasia | 1 (2%) | 5 (10%) | 1 (2%) | 2 (4%) |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Epididymis | (49) | (49) | (49) | (48) |
| Fibrosis | | | 1 (2%) | |
| Inflammation, chronic | | | 2 (4%) | |
| Penis | (1) | | | |
| Inflammation, chronic active | 1 (100%) | | | |
| Preputial gland | (50) | (47) | (49) | (48) |
| Atrophy | 1 (2%) | | | |
| Hyperplasia | 4 (8%) | 3 (6%) | 5 (10%) | 4 (8%) |
| Inflammation, acute | 2 (4%) | | | 2 (4%) |
| Inflammation, chronic | 17 (34%) | 25 (53%) | 17 (35%) | 23 (48%) |
| Inflammation, chronic active | 5 (10%) | 14 (30%) | 14 (29%) | 5 (10%) |
| Duct, dilatation | | 2 (4%) | | 2 (4%) |
| Prostate | (50) | (48) | (50) | (49) |
| Hemorrhage, chronic | | 1 (2%) | | |
| Hyperplasia, focal | 1 (2%) | 1 (2%) | 4 (8%) | 2 (4%) |
| Inflammation, acute | 2 (4%) | 2 (4%) | | 1 (2%) |
| Inflammation, chronic | 2 (4%) | 1 (2%) | 4 (8%) | 3 (6%) |
| Inflammation, chronic active | 31 (62%) | 29 (60%) | 24 (48%) | 22 (45%) |
| Seminal vesicle | (50) | (47) | (50) | (48) |
| Dilatation | | | 1 (2%) | |
| Fibrosis | | | | 1 (2%) |
| Inflammation, acute | | 1 (2%) | 1 (2%) | |
| Inflammation, chronic | 1 (2%) | | | 1 (2%) |
| Inflammation, chronic active | 1 (2%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Mineralization | | | | 1 (2%) |
| Testes | (49) | (49) | (49) | (48) |
| Atrophy | 2 (4%) | | | |
| Necrosis | 1 (2%) | | | |
| Thrombosis | | | 1 (2%) | |
| Bilateral, interstitial cell, hyperplasia | 3 (6%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Interstitial cell, hyperplasia | 9 (18%) | 6 (12%) | 6 (12%) | 4 (8%) |

TABLE A5

Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|---------|----------|
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Depletion cellular | 2 (4%) | 4 (8%) | 3 (6%) | 1 (2%) |
| Fibrosis | | | 1 (2%) | 1 (2%) |
| Hemorrhage | | 1 (2%) | | |
| Lymph node | (20) | (25) | (20) | (23) |
| Iliac, hyperplasia, lymphoid | 1 (5%) | 1 (4%) | | |
| Iliac, infiltration cellular, plasma cell | 1 (5%) | | | |
| Mediastinal, congestion | | 5 (20%) | | 4 (17%) |
| Mediastinal, ectasia | | | 1 (5%) | |
| Mediastinal, hemorrhage | 1 (5%) | 1 (4%) | 2 (10%) | |
| Mediastinal, hyperplasia, lymphoid | | | | 1 (4%) |
| Mediastinal, pigmentation | | | 1 (5%) | |
| Pancreatic, congestion | | | 1 (5%) | 2 (9%) |
| Pancreatic, edema | | | | 1 (4%) |
| Pancreatic, hyperplasia, lymphoid | | | 1 (5%) | |
| Pancreatic, inflammation, chronic active | | | | 1 (4%) |
| Pancreatic, necrosis | | | 1 (5%) | |
| Pancreatic, pigmentation | | | 1 (5%) | |
| Renal, congestion | 1 (5%) | | 1 (5%) | 3 (13%) |
| Renal, edema | | | 1 (5%) | |
| Renal, fibrosis | | 1 (4%) | | |
| Renal, hyperplasia, lymphoid | | | 2 (10%) | |
| Renal, pigmentation | | | 1 (5%) | 4 (17%) |
| Lymph node, mandibular | (50) | (50) | (50) | (50) |
| Congestion | | 1 (2%) | 1 (2%) | |
| Ectasia | 4 (8%) | 3 (6%) | 2 (4%) | 3 (6%) |
| Hyperplasia, lymphoid | | | 1 (2%) | |
| Inflammation, chronic active | | 1 (2%) | | |
| Lymph node, mesenteric | (50) | (47) | (50) | (48) |
| Congestion | | 2 (4%) | | 1 (2%) |
| Ectasia | 2 (4%) | 3 (6%) | 2 (4%) | 1 (2%) |
| Fibrosis | | | 2 (4%) | |
| Hemorrhage | | 1 (2%) | | 1 (2%) |
| Inflammation, acute | 1 (2%) | | | |
| Necrosis | | 3 (6%) | | |
| Spleen | (49) | (48) | (50) | (49) |
| Atrophy | | | 1 (2%) | |
| Congestion | | 1 (2%) | | 1 (2%) |
| Fibrosis | 14 (29%) | 11 (23%) | 9 (18%) | 12 (24%) |
| Hematopoietic cell proliferation | 1 (2%) | 1 (2%) | | 1 (2%) |
| Hyperplasia, focal | | | 1 (2%) | |
| Necrosis | 4 (8%) | 2 (4%) | 1 (2%) | |
| Pigmentation | | | | 2 (4%) |
| Thrombosis | | 1 (2%) | | |
| Thymus | (50) | (49) | (48) | (50) |
| Cyst | 1 (2%) | | | |
| Ectopic parathyroid gland | | | | 1 (2%) |
| Fibrosis | | 1 (2%) | | |
| Hemorrhage | | 1 (2%) | | 1 (2%) |

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|----------|----------|
| Integumentary System | | | | |
| Mammary gland | (49) | (48) | (50) | (49) |
| Concretion | | 1 (2%) | | |
| Galactocele | | | 1 (2%) | |
| Hyperplasia | 1 (2%) | 3 (6%) | 2 (4%) | 3 (6%) |
| Duct, dilatation | 14 (29%) | 16 (33%) | 12 (24%) | 15 (31%) |
| Skin | (50) | (50) | (50) | (50) |
| Cyst epithelial inclusion | | | 2 (4%) | |
| Hyperkeratosis | | | 1 (2%) | |
| Hyperplasia, squamous | | 1 (2%) | 1 (2%) | |
| Inflammation, acute | | 1 (2%) | | |
| Necrosis | | | 1 (2%) | |
| Epidermis, degeneration | | | | 1 (2%) |
| Subcutaneous tissue, inflammation, chronic active | | | 1 (2%) | |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Fibrous osteodystrophy | 2 (4%) | 1 (2%) | 4 (8%) | 6 (12%) |
| Hyperostosis | | 1 (2%) | | |
| Osteomalacia | | | | 1 (2%) |
| Osteopetrosis | 1 (2%) | | 2 (4%) | |
| Nervous System | | | | |
| Brain | (50) | (50) | (48) | (50) |
| Hemorrhage | | | 1 (2%) | |
| Hydrocephalus | 1 (2%) | | | |
| Inflammation, acute | | | | 1 (2%) |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Congestion | | 1 (2%) | | 2 (4%) |
| Hemorrhage | | | 2 (4%) | 2 (4%) |
| Hyperplasia, lymphoid | 1 (2%) | 1 (2%) | | |
| Infiltration cellular, histiocyte | 6 (12%) | 4 (8%) | 9 (18%) | 9 (18%) |
| Inflammation, chronic | 8 (16%) | 10 (20%) | 12 (24%) | 9 (18%) |
| Metaplasia, osseous | | | | 1 (2%) |
| Alveolar epithelium, hyperplasia | | 3 (6%) | | 3 (6%) |
| Nose | (50) | (50) | (49) | (50) |
| Cyst | | 1 (2%) | 1 (2%) | |
| Cyst epithelial inclusion | | | | 1 (2%) |
| Inflammation, chronic | | | 1 (2%) | |
| Inflammation, chronic active | 26 (52%) | 18 (36%) | 21 (43%) | 25 (50%) |
| Polyp inflammatory | | | | 1 (2%) |
| Nasolacrimal duct, cyst | | | 1 (2%) | 1 (2%) |
| Nasolacrimal duct, inflammation, acute | 1 (2%) | | | 1 (2%) |
| Squamous epithelium, nasolacrimal duct, hyperplasia | | 1 (2%) | | |
| Special Senses System | | | | |
| Eye | | (1) | | |
| Atrophy | | 1 (100%) | | |

TABLE A5

Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--------------------------------------|----------|----------|----------|-----------|
| Urinary System | | | | |
| Kidney | (50) | (48) | (50) | (49) |
| Atrophy | | | 1 (2%) | |
| Cyst | 3 (6%) | 3 (6%) | 13 (26%) | 10 (20%) |
| Developmental malformation | 2 (4%) | | | |
| Hydronephrosis | 3 (6%) | 1 (2%) | | 2 (4%) |
| Inflammation, acute | | | | 1 (2%) |
| Nephropathy | 47 (94%) | 47 (98%) | 49 (98%) | 49 (100%) |
| Pigmentation | | | | 1 (2%) |
| Artery, inflammation, acute | 1 (2%) | | | |
| Artery, inflammation, chronic active | 1 (2%) | | | |
| Capsule, hemorrhage, chronic | | 1 (2%) | | |
| Pelvis, inflammation, acute | | | | 1 (2%) |
| Renal tubule, hyperplasia | 1 (2%) | | 4 (8%) | 7 (14%) |
| Urinary bladder | (50) | (47) | (50) | (49) |
| Hemorrhage | | 1 (2%) | 1 (2%) | 1 (2%) |
| Inflammation, chronic | 4 (8%) | | 1 (2%) | 1 (2%) |

APPENDIX B

SUMMARY OF LESIONS IN FEMALE F344/N RATS IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

| | | |
|-----------------|---|------------|
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TABLE B1**Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine^a**

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|---------|---------|---------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 3 | 8 | 7 | 2 |
| Natural deaths | 15 | 5 | 14 | 22 |
| Survivors | | | | |
| Terminal sacrifice | 32 | 37 | 29 | 26 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| Alimentary System | | | | |
| Esophagus | (50) | (50) | (50) | (50) |
| Schwannoma malignant, metastatic, uterus | | 1 (2%) | | |
| Intestine large, colon | (50) | (50) | (50) | (50) |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Intestine large, cecum | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Intestine small, duodenum | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Carcinoma, metastatic, uterus | | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Intestine small, jejunum | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Intestine small, ileum | (50) | (49) | (50) | (50) |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Liver | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Carcinoma, metastatic, uterus | | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Hepatocellular adenoma | 1 (2%) | | 1 (2%) | |
| Mesentery | (9) | (11) | (7) | (12) |
| Carcinoma, metastatic, uterus | | 1 (9%) | | |
| Fibrous histiocytoma | 1 (11%) | | | |
| Schwannoma malignant, metastatic, uterus | | 1 (9%) | | |
| Oral mucosa | (2) | (1) | | (2) |
| Pharyngeal, squamous cell carcinoma | 2 (100%) | | | |
| Pharyngeal, squamous cell papilloma | | | | 1 (50%) |
| Pancreas | (49) | (50) | (50) | (50) |
| Carcinoma | | 2 (4%) | | |
| Carcinoma, metastatic, uterus | | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Acinus, adenoma | | 1 (2%) | | 1 (2%) |
| Salivary glands | (50) | (50) | (50) | (50) |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, uterus | | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Tongue | | | (1) | (2) |
| Squamous cell papilloma | | | | 1 (50%) |

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|----------|----------|----------|----------|
| Cardiovascular System | | | | |
| Heart | (49) | (50) | (50) | (50) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Endocrine System | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Adrenal medulla | (50) | (50) | (50) | (49) |
| Pheochromocytoma benign | 2 (4%) | | 1 (2%) | |
| Bilateral, pheochromocytoma benign | 1 (2%) | | | |
| Islets, pancreatic | (49) | (50) | (50) | (50) |
| Adenoma | 1 (2%) | | 1 (2%) | |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Parathyroid gland | (48) | (50) | (48) | (50) |
| Pituitary gland | (49) | (50) | (50) | (50) |
| Pars distalis, adenoma | 17 (35%) | 12 (24%) | 18 (36%) | 15 (30%) |
| Pars distalis, adenoma, multiple | 1 (2%) | | | |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Bilateral, C-cell, adenoma | | 1 (2%) | | |
| C-cell, adenoma | 3 (6%) | 2 (4%) | 2 (4%) | |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Clitoral gland | (47) | (48) | (50) | (49) |
| Adenoma | 2 (4%) | 3 (6%) | | 1 (2%) |
| Carcinoma | | 1 (2%) | 1 (2%) | 2 (4%) |
| Bilateral, adenoma | | | 1 (2%) | |
| Ovary | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Granulosa-theca tumor malignant | | | 1 (2%) | |
| Uterus | (50) | (50) | (50) | (50) |
| Carcinoma | | 1 (2%) | | |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Polyp stromal | 4 (8%) | 7 (14%) | 9 (18%) | 7 (14%) |
| Polyp stromal, multiple | | | | 1 (2%) |
| Sarcoma stromal | 1 (2%) | | | |
| Schwannoma malignant, metastatic, uterus | | 1 (2%) | | |
| Vagina | | | | (1) |
| Lipoma | | | | 1 (100%) |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Lymph node | (7) | (9) | (15) | (19) |
| Mediastinal, carcinoma, metastatic, kidney | | 1 (11%) | | |
| Mediastinal, carcinoma, metastatic, pancreas | | 1 (11%) | | |
| Mediastinal, fibrous histiocytoma, metastatic, mesentery | 1 (14%) | | | |

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|----------|----------|----------|----------|
| Hematopoietic System (continued) | | | | |
| Lymph node, mandibular | (49) | (50) | (50) | (50) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Lymph node, mesenteric | (49) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Carcinoma, metastatic, uterus | | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, mesentery | 1 (2%) | | | |
| Spleen | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Carcinoma, metastatic, uterus | | 1 (2%) | | |
| Thymus | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Integumentary System | | | | |
| Mammary gland | (50) | (50) | (50) | (50) |
| Adenoma | 2 (4%) | 1 (2%) | 1 (2%) | |
| Carcinoma | 1 (2%) | 2 (4%) | 1 (2%) | 1 (2%) |
| Fibroadenoma | 19 (38%) | 15 (30%) | 14 (28%) | 18 (36%) |
| Fibroadenoma, multiple | 8 (16%) | 10 (20%) | 6 (12%) | 2 (4%) |
| Sarcoma | 1 (2%) | | | |
| Skin | (50) | (50) | (50) | (50) |
| Basal cell adenoma | | 1 (2%) | | |
| Keratoacanthoma | | | | 1 (2%) |
| Trichoepithelioma | | | | 1 (2%) |
| Musculoskeletal System | | | | |
| Skeletal muscle | (2) | (1) | | |
| Carcinoma, metastatic, uterus | | 1 (100%) | | |
| Abdominal, fibrous histiocytoma, metastatic, mesentery | 1 (50%) | | | |
| Abdominal, lipoma | 1 (50%) | | | |
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Astrocytoma malignant | 2 (4%) | | | |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | 1 (2%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Carcinoma, metastatic, clitoral gland | | | | 1 (2%) |
| Carcinoma, metastatic, kidney | | 1 (2%) | | |
| Carcinoma, metastatic, mammary gland | | | 1 (2%) | |
| Carcinoma, metastatic, pancreas | | 2 (4%) | | |
| Carcinoma, metastatic, uterus | | 1 (2%) | | |
| Nose | (50) | (50) | (50) | (50) |
| Pleura | | (1) | | |
| Carcinoma, metastatic, kidney | | 1 (100%) | | |
| Trachea | (50) | (50) | (50) | (50) |

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|----------|----------|
| Special Senses System | | | | |
| Zymbal's gland | | (1) | | (1) |
| Carcinoma | | 1 (100%) | | 1 (100%) |
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Transitional epithelium, carcinoma | | 1 (2%) | | |
| Urinary bladder | (50) | (50) | (50) | (50) |
| Systemic Lesions | | | | |
| Multiple organs ^b | (50) | (50) | (50) | (50) |
| Leukemia mononuclear | 12 (24%) | 16 (32%) | 22 (44%) | 23 (46%) |
| Lymphoma malignant | 1 (2%) | | | 1 (2%) |
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^c | 45 | 42 | 45 | 44 |
| Total primary neoplasms | 84 | 78 | 80 | 80 |
| Total animals with benign neoplasms | 39 | 34 | 35 | 35 |
| Total benign neoplasms | 63 | 54 | 55 | 52 |
| Total animals with malignant neoplasms | 21 | 22 | 23 | 28 |
| Total malignant neoplasms | 21 | 24 | 25 | 28 |
| Total animals with metastatic neoplasms | 1 | 5 | 1 | 1 |
| Total metastatic neoplasms | 13 | 36 | 1 | 1 |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

| | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 | 4 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| Number of Days on Study | 9 | 9 | 0 | 8 | 9 | 2 | 3 | 4 | 6 | 6 | 7 | 7 | 8 | 8 | 9 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 9 | 3 | 3 | 8 | 6 | 2 | 6 | 9 | 1 | 7 | 1 | 3 | 1 | 7 | 6 | 7 | 7 | 2 | 9 | 9 | 9 | 9 | 9 |
| | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Carcass ID Number | 2 | 3 | 5 | 5 | 2 | 2 | 3 | 2 | 6 | 6 | 6 | 1 | 4 | 2 | 4 | 4 | 5 | 1 | 1 | 1 | 2 | 2 | 2 |
| | 3 | 3 | 9 | 0 | 9 | 0 | 9 | 1 | 0 | 1 | 2 | 9 | 0 | 5 | 6 | 9 | 5 | 8 | 6 | 7 | 2 | 4 | 6 |
| | | | | | | | | | | | | | | | | | | | | | | | 8 |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | + | | | + | | | | | + | + | | | |
| Fibrous histiocytoma | | | | | | | | | | | | | | | | | | | | | | | |
| Oral mucosa | + | | | | | | | | | | | | | | | | | | + | | | | |
| Pharyngeal, squamous cell carcinoma | X | | | | | | | | | | | | | | | | | | X | | | | |
| Pancreas | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | |
| Bilateral, pheochromocytoma benign | | | | | | | | | | X | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | |
| Fibrous histiocytoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | M | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Pars distalis, adenoma | | | | X | X | | | X | X | | | | X | | X | X | X | | | | X | | X |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | X | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | X | | X | | | | | | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | M | + | M | M | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | X | | | | | | | | | | | | | | | | | X |

X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Days on Study | 4 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| | 8 | 3 | 4 | 7 | 1 | 4 | 5 | 6 | 6 | 8 | 9 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 8 | 3 | 6 | 0 | 1 | 2 | 0 | 6 | 6 | 2 | 5 | 7 | 8 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| Carcass ID Number | 2 | 2 | 2 | 3 | 2 | 3 | 2 | 2 | 3 | 3 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 8 | 7 | 8 | 0 | 8 | 1 | 7 | 9 | 1 | 0 | 6 | 7 | 1 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 8 | 8 | 8 | 8 | |
| | 0 | 7 | 4 | 0 | 8 | 2 | 8 | 9 | 5 | 1 | 7 | 4 | 1 | 6 | 8 | 9 | 0 | 2 | 3 | 6 | 9 | 1 | 2 | 3 | 5 |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, kidney | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, pancreas | | | | X | | X | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, uterus | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Pleura | | | | | | | | | | + | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, kidney | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zymbal's gland | | | | + | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Carcinoma, metastatic, pancreas | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Transitional epithelium, carcinoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Leukemia mononuclear | | | | X | | | | | | X | X | X | | X | | X | X | | | X | X | | X | | |

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
|---------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-----------------------------|--|
| Number of Days on Study | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | | |
| Carcass ID Number | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | Total Tissues/ Tumors | |
| | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | 6 | 6 | 6 | |
| | 4 | 5 | 6 | 8 | 9 | 0 | 1 | 2 | 3 | 5 | 6 | 8 | 1 | 2 | 3 | 4 | 7 | 9 | 2 | 5 | 8 | 0 | 1 | 4 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | X | 1 | |
| Mesentery | | | | | | + | | | | | + | | | | | | | | | | + | | | 7 | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Tongue | | | | | | | | | | | | | | | | | | | | | | + | | 1 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | X | | | | | | | | 1 | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | 48 | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Pars distalis, adenoma | X | | | | | X | | | | | | X | | | | X | X | X | X | X | X | X | X | 18 | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| C-cell, adenoma | | | | | | | | | | | | | | | X | | | | | | | | | 2 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Bilateral, adenoma | | | | | | | | | | | | | | | | | | | | | | X | | 1 | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Granulosa-theca tumor malignant | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Polyp stromal | | | | X | | X | | X | | | | | | | | X | | X | X | | | | | 9 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Lymph node | | | | | | | | | | | | | | + | + | + | | + | | | | | | 15 | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |

TABLE B2

Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Days on Study | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | 9 | 2 | 4 | 6 | 7 | 8 | 8 | 0 | 2 | 6 | 7 | 8 | 9 | 9 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 6 | 1 | 9 | 1 | 3 | 0 | 6 | 5 | 4 | 5 | 1 | 7 | 8 | 9 | 0 | 3 | 7 | 7 | 1 | 8 | 1 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Carcass ID Number | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 3 | 4 | 2 | 5 | 1 | 5 | 6 | 5 | 5 | 3 | 5 | 3 | 4 | 5 | 6 | 2 | 1 | 4 | 5 | 4 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 9 | 8 | 7 | 3 | 7 | 9 | 3 | 1 | 4 | 4 | 6 | 7 | 6 | 7 | 2 | 0 | 8 | 5 | 0 | 0 | 6 | 9 | 1 | 2 | 3 | 3 | 3 | 3 |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Fibroadenoma | | | | | | X | | | | | X | | | | | | | | X | | | X | | X | | X | | |
| Fibroadenoma, multiple | | | | | | | | | | | | | X | | | | | X | | | | | | | | X | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Carcinoma, metastatic, mammary gland | | | | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | X | X | X | | X | X | X | X | | X | | | | X | X | X | | | X | X | X | | | | X | X | | |

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|--------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-----------------------------|
| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| Number of Days on Study | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | |
| Carcass ID Number | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | Total Tissues/ Tumors |
| | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | 6 | 6 | 6 | |
| | 4 | 5 | 6 | 8 | 9 | 0 | 1 | 2 | 3 | 5 | 6 | 8 | 1 | 2 | 3 | 4 | 7 | 9 | 2 | 5 | 8 | 0 | 1 | 4 | 5 |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Fibroadenoma | | | X | X | | | | X | | X | | X | | | | X | X | | X | | | | | X | 14 |
| Fibroadenoma, multiple | | | | | | | | | | | | | | X | | | | X | | X | | | | | 6 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, mammary gland | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | + | | | | | | | | | | | | | 1 |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | | | X | | X | X | | | | | X | | X | | | | X | | | | | | | 22 |

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

[illegible]

TABLE B3

Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|-------------|----------------|----------------|-------------|
| Adrenal Medulla: Benign Pheochromocytoma | | | | |
| Overall rate ^a | 3/50 (6%) | 0/50 (0%) | 1/50 (2%) | 0/49 (0%) |
| Adjusted rate ^b | 6.7% | 0.0% | 2.3% | 0.0% |
| Terminal rate ^c | 2/32 (6%) | 0/37 (0%) | 1/29 (3%) | 0/25 (0%) |
| First incidence (days) | 667 | — ^e | 729 (T) | — |
| Poly-3 test ^d | P=0.094N | P=0.114N | P=0.311N | P=0.140N |
| Clitoral Gland: Adenoma | | | | |
| Overall rate | 2/47 (4%) | 3/48 (6%) | 1/50 (2%) | 1/49 (2%) |
| Adjusted rate | 4.7% | 6.8% | 2.3% | 2.5% |
| Terminal rate | 1/32 (3%) | 3/36 (8%) | 1/29 (3%) | 1/25 (4%) |
| First incidence (days) | 622 | 729 (T) | 729 (T) | 729 (T) |
| Poly-3 test | P=0.295N | P=0.521 | P=0.487N | P=0.522N |
| Clitoral Gland: Adenoma or Carcinoma | | | | |
| Overall rate | 2/47 (4%) | 4/48 (8%) | 2/50 (4%) | 3/49 (6%) |
| Adjusted rate | 4.7% | 9.0% | 4.6% | 7.6% |
| Terminal rate | 1/32 (3%) | 3/36 (8%) | 1/29 (3%) | 3/25 (12%) |
| First incidence (days) | 622 | 728 | 707 | 729 (T) |
| Poly-3 test | P=0.483 | P=0.359 | P=0.680N | P=0.472 |
| Mammary Gland: Fibroadenoma | | | | |
| Overall rate | 27/50 (54%) | 25/50 (50%) | 20/50 (40%) | 20/50 (40%) |
| Adjusted rate | 58.5% | 53.7% | 44.6% | 47.3% |
| Terminal rate | 18/32 (56%) | 19/37 (51%) | 15/29 (52%) | 15/26 (58%) |
| First incidence (days) | 596 | 666 | 580 | 589 |
| Poly-3 test | P=0.139N | P=0.398N | P=0.126N | P=0.193N |
| Mammary Gland: Fibroadenoma or Adenoma | | | | |
| Overall rate | 27/50 (54%) | 25/50 (50%) | 20/50 (40%) | 20/50 (40%) |
| Adjusted rate | 58.5% | 53.7% | 44.6% | 47.3% |
| Terminal rate | 18/32 (56%) | 19/37 (51%) | 15/29 (52%) | 15/26 (58%) |
| First incidence (days) | 596 | 666 | 580 | 589 |
| Poly-3 test | P=0.139N | P=0.398N | P=0.126N | P=0.193N |
| Mammary Gland: Adenoma or Carcinoma | | | | |
| Overall rate | 3/50 (6%) | 3/50 (6%) | 2/50 (4%) | 1/50 (2%) |
| Adjusted rate | 6.8% | 6.5% | 4.5% | 2.5% |
| Terminal rate | 2/32 (6%) | 1/37 (3%) | 0/29 (0%) | 1/26 (4%) |
| First incidence (days) | 717 | 650 | 699 | 729 (T) |
| Poly-3 test | P=0.223N | P=0.646N | P=0.503N | P=0.337N |
| Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma | | | | |
| Overall rate | 27/50 (54%) | 26/50 (52%) | 21/50 (42%) | 21/50 (42%) |
| Adjusted rate | 58.5% | 55.5% | 46.7% | 49.6% |
| Terminal rate | 18/32 (56%) | 19/37 (51%) | 15/29 (52%) | 16/26 (62%) |
| First incidence (days) | 596 | 650 | 580 | 589 |
| Poly-3 test | P=0.191N | P=0.468N | P=0.174N | P=0.262N |
| Pancreas: Adenoma or Carcinoma | | | | |
| Overall rate | 0/49 (0%) | 3/50 (6%) | 0/50 (0%) | 1/50 (2%) |
| Adjusted rate | 0.0% | 6.4% | 0.0% | 2.5% |
| Terminal rate | 0/32 (0%) | 1/37 (3%) | 0/29 (0%) | 1/26 (4%) |
| First incidence (days) | — | 546 | — | 729 (T) |
| Poly-3 test | P=0.609 | P=0.131 | — ^f | P=0.486 |

TABLE B3

Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|-------------|-------------|-------------|-------------|
| Pituitary Gland (Pars Distalis): Adenoma | | | | |
| Overall rate | 18/49 (37%) | 12/50 (24%) | 18/50 (36%) | 15/50 (30%) |
| Adjusted rate | 39.9% | 25.8% | 40.4% | 35.8% |
| Terminal rate | 10/31 (32%) | 8/37 (22%) | 13/29 (45%) | 10/26 (39%) |
| First incidence (days) | 588 | 642 | 671 | 634 |
| Poly-3 test | P=0.509 | P=0.110N | P=0.565 | P=0.431N |
| Thyroid Gland (C-cell): Adenoma | | | | |
| Overall rate | 3/50 (6%) | 3/50 (6%) | 2/50 (4%) | 0/50 (0%) |
| Adjusted rate | 6.7% | 6.5% | 4.6% | 0.0% |
| Terminal rate | 1/32 (3%) | 2/37 (5%) | 1/29 (3%) | 0/26 (0%) |
| First incidence (days) | 687 | 695 | 707 | — |
| Poly-3 test | P=0.087N | P=0.649N | P=0.506N | P=0.135N |
| Uterus: Stromal Polyp | | | | |
| Overall rate | 4/50 (8%) | 7/50 (14%) | 9/50 (18%) | 8/50 (16%) |
| Adjusted rate | 9.0% | 15.3% | 20.4% | 19.1% |
| Terminal rate | 4/32 (13%) | 7/37 (19%) | 6/29 (21%) | 5/26 (19%) |
| First incidence (days) | 729 (T) | 729 (T) | 687 | 503 |
| Poly-3 test | P=0.125 | P=0.278 | P=0.111 | P=0.147 |
| Uterus: Stromal Polyp or Stromal Sarcoma | | | | |
| Overall rate | 5/50 (10%) | 7/50 (14%) | 9/50 (18%) | 8/50 (16%) |
| Adjusted rate | 11.1% | 15.3% | 20.4% | 19.1% |
| Terminal rate | 4/32 (13%) | 7/37 (19%) | 6/29 (21%) | 5/26 (19%) |
| First incidence (days) | 493 | 729 (T) | 687 | 503 |
| Poly-3 test | P=0.177 | P=0.390 | P=0.180 | P=0.227 |
| All Organs: Mononuclear Cell Leukemia | | | | |
| Overall rate | 12/50 (24%) | 16/50 (32%) | 22/50 (44%) | 23/50 (46%) |
| Adjusted rate | 26.5% | 34.3% | 45.4% | 48.7% |
| Terminal rate | 8/32 (25%) | 12/37 (32%) | 8/29 (28%) | 5/26 (19%) |
| First incidence (days) | 636 | 546 | 496 | 380 |
| Poly-3 test | P=0.013 | P=0.279 | P=0.043 | P=0.020 |
| All Organs: Benign Neoplasms | | | | |
| Overall rate | 39/50 (78%) | 34/50 (68%) | 35/50 (70%) | 35/50 (70%) |
| Adjusted rate | 81.6% | 72.5% | 77.1% | 78.6% |
| Terminal rate | 24/32 (75%) | 27/37 (73%) | 25/29 (86%) | 23/26 (89%) |
| First incidence (days) | 588 | 642 | 580 | 503 |
| Poly-3 test | P=0.511N | P=0.203N | P=0.385N | P=0.459N |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 21/50 (42%) | 23/50 (46%) | 23/50 (46%) | 28/50 (56%) |
| Adjusted rate | 44.3% | 46.7% | 47.4% | 59.3% |
| Terminal rate | 13/32 (41%) | 13/37 (35%) | 8/29 (28%) | 10/26 (39%) |
| First incidence (days) | 399 | 488 | 496 | 380 |
| Poly-3 test | P=0.077 | P=0.486 | P=0.459 | P=0.100 |

TABLE B3
Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|-------------|-------------|-------------|-------------|
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 45/50 (90%) | 43/50 (86%) | 45/50 (90%) | 44/50 (88%) |
| Adjusted rate | 91.2% | 86.0% | 91.7% | 91.0% |
| Terminal rate | 28/32 (88%) | 30/37 (81%) | 26/29 (90%) | 23/26 (89%) |
| First incidence (days) | 399 | 488 | 496 | 380 |
| Poly-3 test | P=0.452 | P=0.307N | P=0.613 | P=0.627N |

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pancreas, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

^f Value of statistic cannot be computed.

TABLE B4
Historical Incidence of Leukemias in Untreated Female F344/N Rats^a

| | | Incidence in Controls |
|-------------------------------------|--|-----------------------|
| Overall Historical Incidence | | |
| Total | | 102/330 (30.9%) |
| Standard deviation | | 10.0% |
| Range | | 16%-44% |

^a Data as of 1 August 1997; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemias

TABLE B5

Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine^a

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|----------------------------------|----------|----------|----------|----------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 3 | 8 | 7 | 2 |
| Natural deaths | 15 | 5 | 14 | 22 |
| Survivors | | | | |
| Terminal sacrifice | 32 | 37 | 29 | 26 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| Alimentary System | | | | |
| Intestine large, colon | (50) | (50) | (50) | (50) |
| Hyperplasia, lymphoid | | | 1 (2%) | |
| Parasite metazoan | 3 (6%) | 3 (6%) | 3 (6%) | 1 (2%) |
| Intestine large, rectum | (50) | (50) | (50) | (50) |
| Parasite metazoan | 1 (2%) | 2 (4%) | 1 (2%) | 2 (4%) |
| Intestine large, cecum | (50) | (50) | (50) | (50) |
| Inflammation, chronic | | | | 1 (2%) |
| Inflammation, chronic active | | | 1 (2%) | |
| Parasite metazoan | | | 1 (2%) | |
| Ulcer | | 1 (2%) | | |
| Intestine small, duodenum | (50) | (50) | (50) | (50) |
| Ectopic pancreas | 1 (2%) | | | |
| Inflammation, chronic active | | | 1 (2%) | |
| Intestine small, ileum | (50) | (49) | (50) | (50) |
| Hyperplasia, lymphoid | 3 (6%) | 2 (4%) | 2 (4%) | 5 (10%) |
| Inflammation, chronic active | | | | 1 (2%) |
| Liver | (50) | (50) | (50) | (50) |
| Angiectasis | 2 (4%) | 2 (4%) | 3 (6%) | 2 (4%) |
| Basophilic focus | 38 (76%) | 28 (56%) | 11 (22%) | |
| Clear cell focus | 4 (8%) | 9 (18%) | 11 (22%) | 16 (32%) |
| Congestion | 4 (8%) | 1 (2%) | 3 (6%) | 2 (4%) |
| Developmental malformation | 1 (2%) | 2 (4%) | 1 (2%) | |
| Eosinophilic focus | 19 (38%) | 24 (48%) | 22 (44%) | 15 (30%) |
| Fibrosis | 1 (2%) | 1 (2%) | | |
| Hematopoietic cell proliferation | | 1 (2%) | 1 (2%) | 2 (4%) |
| Hemorrhage | | 1 (2%) | 1 (2%) | |
| Hepatodiaphragmatic nodule | 9 (18%) | 8 (16%) | 3 (6%) | 3 (6%) |
| Inflammation, chronic active | 9 (18%) | 1 (2%) | 2 (4%) | 4 (8%) |
| Mitotic alteration | 1 (2%) | | | 1 (2%) |
| Mixed cell focus | 2 (4%) | 4 (8%) | 1 (2%) | 5 (10%) |
| Necrosis | 6 (12%) | 1 (2%) | 1 (2%) | |
| Pigmentation | 6 (12%) | 2 (4%) | 6 (12%) | 17 (34%) |
| Tension lipidosis | 3 (6%) | 1 (2%) | | |
| Vacuolization cytoplasmic | 10 (20%) | 7 (14%) | 9 (18%) | 18 (36%) |
| Bile duct, hyperplasia | 20 (40%) | 29 (58%) | 34 (68%) | 29 (58%) |
| Capsule, inflammation, chronic | | | | 2 (4%) |
| Centrilobular, cytomegaly | | 1 (2%) | 4 (8%) | 20 (40%) |
| Centrilobular, degeneration | 1 (2%) | 2 (4%) | 2 (4%) | 7 (14%) |
| Centrilobular, necrosis | 1 (2%) | 2 (4%) | 1 (2%) | |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--------------------------------------|----------|----------|----------|----------|
| Alimentary System (continued) | | | | |
| Mesentery | (9) | (11) | (7) | (12) |
| Ectopic spleen | | | 1 (14%) | |
| Inflammation | | | | 1 (8%) |
| Fat, necrosis | 8 (89%) | 9 (82%) | 6 (86%) | 11 (92%) |
| Oral mucosa | (2) | (1) | | (2) |
| Pharyngeal, hyperplasia | | | | 1 (50%) |
| Pharyngeal, inflammation, acute | | 1 (100%) | | |
| Pancreas | (49) | (50) | (50) | (50) |
| Atrophy | 22 (45%) | 14 (28%) | 13 (26%) | 14 (28%) |
| Cytoplasmic alteration | 1 (2%) | | | |
| Ectopic liver | | 2 (4%) | 2 (4%) | 3 (6%) |
| Hyperplasia | | 3 (6%) | 2 (4%) | |
| Inflammation, chronic | | | 1 (2%) | 2 (4%) |
| Salivary glands | (50) | (50) | (50) | (50) |
| Atrophy | | 2 (4%) | 3 (6%) | 1 (2%) |
| Cytoplasmic alteration | | 1 (2%) | | 1 (2%) |
| Inflammation, chronic | | 2 (4%) | | |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Fibrosis | | | 1 (2%) | |
| Hyperkeratosis | 1 (2%) | | | |
| Inflammation, acute | 1 (2%) | | 1 (2%) | |
| Inflammation, chronic | | | 1 (2%) | 1 (2%) |
| Inflammation, chronic active | 2 (4%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Ulcer | 3 (6%) | 3 (6%) | 4 (8%) | 4 (8%) |
| Epithelium, hyperplasia, squamous | 2 (4%) | 2 (4%) | 2 (4%) | 1 (2%) |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Erosion | 6 (12%) | 9 (18%) | 9 (18%) | 7 (14%) |
| Inflammation, chronic | | | | 1 (2%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Mineralization | | | 2 (4%) | |
| Ulcer | 1 (2%) | 1 (2%) | 3 (6%) | |
| Tongue | | | (1) | (2) |
| Epithelium, hyperplasia | | | 1 (100%) | 1 (50%) |
| Cardiovascular System | | | | |
| Heart | (49) | (50) | (50) | (50) |
| Cardiomyopathy | 42 (86%) | 43 (86%) | 43 (86%) | 36 (72%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Mineralization | 1 (2%) | | | |
| Thrombosis | | | 2 (4%) | 1 (2%) |
| Endocrine System | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Accessory adrenal cortical nodule | 1 (2%) | | | |
| Atrophy | | | 1 (2%) | |
| Congestion | | 1 (2%) | | 1 (2%) |
| Cyst | | 1 (2%) | | 1 (2%) |
| Hematopoietic cell proliferation | 1 (2%) | | | |
| Hemorrhage | 1 (2%) | | | |
| Hyperplasia | 11 (22%) | 12 (24%) | 9 (18%) | 6 (12%) |
| Vacuolization cytoplasmic | 6 (12%) | 8 (16%) | 6 (12%) | 3 (6%) |

TABLE B5

Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|-------------------------------------|----------|----------|----------|----------|
| Endocrine System (continued) | | | | |
| Adrenal medulla | (50) | (50) | (50) | (49) |
| Hyperplasia | 5 (10%) | 7 (14%) | 8 (16%) | 2 (4%) |
| Necrosis | | 1 (2%) | | |
| Islets, pancreatic | (49) | (50) | (50) | (50) |
| Hyperplasia | | | 1 (2%) | 1 (2%) |
| Parathyroid gland | (48) | (50) | (48) | (50) |
| Hyperplasia | 1 (2%) | | | |
| Pituitary gland | (49) | (50) | (50) | (50) |
| Pigmentation | | | 1 (2%) | |
| Pars distalis, angiectasis | 11 (22%) | 9 (18%) | 12 (24%) | 4 (8%) |
| Pars distalis, cyst | 16 (33%) | 18 (36%) | 20 (40%) | 8 (16%) |
| Pars distalis, ectasia | | 1 (2%) | | |
| Pars distalis, hemorrhage | 1 (2%) | | | |
| Pars distalis, hyperplasia | 22 (45%) | 29 (58%) | 21 (42%) | 18 (36%) |
| Pars intermedia, hyperplasia | 1 (2%) | | | |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Ultimobranchial cyst | | 3 (6%) | | 1 (2%) |
| C-cell, hyperplasia | 16 (32%) | 17 (34%) | 13 (26%) | 10 (20%) |
| Follicular cell, hyperplasia | 1 (2%) | | | |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Clitoral gland | (47) | (48) | (50) | (49) |
| Hyperplasia | 1 (2%) | 2 (4%) | 1 (2%) | 2 (4%) |
| Inflammation, acute | 1 (2%) | 2 (4%) | | |
| Inflammation, chronic | 3 (6%) | 1 (2%) | 5 (10%) | 2 (4%) |
| Inflammation, chronic active | 1 (2%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Vacuolization cytoplasmic | | | | 1 (2%) |
| Bilateral, inflammation, acute | | | 1 (2%) | |
| Duct, ectasia | 3 (6%) | 5 (10%) | 4 (8%) | 2 (4%) |
| Ovary | (50) | (50) | (50) | (50) |
| Congestion | 1 (2%) | | | |
| Cyst | 3 (6%) | 7 (14%) | 4 (8%) | 2 (4%) |
| Hyperplasia | | 1 (2%) | | |
| Inflammation, chronic | 1 (2%) | | | 1 (2%) |
| Pigmentation | | | 1 (2%) | |
| Bilateral, cyst | | 1 (2%) | | 2 (4%) |
| Uterus | (50) | (50) | (50) | (50) |
| Angiectasis | | 1 (2%) | | |
| Cyst | | 1 (2%) | | 1 (2%) |
| Developmental malformation | | | 1 (2%) | |
| Dilatation | | 1 (2%) | 1 (2%) | 2 (4%) |
| Hemorrhage | | 1 (2%) | | 1 (2%) |
| Hyperplasia | | | | 1 (2%) |
| Hyperplasia, cystic | 6 (12%) | | 5 (10%) | 7 (14%) |
| Inflammation, acute | | | | 1 (2%) |
| Inflammation, chronic | | 1 (2%) | | 1 (2%) |
| Inflammation, chronic active | | 1 (2%) | | |
| Metaplasia, squamous | | | 1 (2%) | |
| Necrosis | 1 (2%) | | | 1 (2%) |
| Cervix, hypertrophy | | | 1 (2%) | |
| Cervix, inflammation, chronic | | | | 1 (2%) |

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|------------------------------------|---------|---------|---------|---------|
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Depletion cellular | 1 (2%) | | 2 (4%) | 2 (4%) |
| Fibrosis | 1 (2%) | 1 (2%) | | |
| Hyperplasia | 3 (6%) | 4 (8%) | | 1 (2%) |
| Hyperplasia, reticulum cell | | 1 (2%) | | |
| Necrosis | | | 1 (2%) | |
| Erythroid cell, hyperplasia | | | 1 (2%) | |
| Myeloid cell, hyperplasia | | 1 (2%) | | |
| Lymph node | (7) | (9) | (15) | (19) |
| Iliac, congestion | 2 (29%) | | | |
| Iliac, ectasia | | | | 2 (11%) |
| Mediastinal, congestion | 3 (43%) | 1 (11%) | 4 (27%) | 1 (5%) |
| Mediastinal, hyperplasia, lymphoid | | | 1 (7%) | |
| Mediastinal, pigmentation | 1 (14%) | | | 1 (5%) |
| Pancreatic, congestion | | | 1 (7%) | |
| Pancreatic, pigmentation | | 1 (11%) | | |
| Renal, congestion | 1 (14%) | 1 (11%) | 1 (7%) | |
| Renal, ectasia | | 1 (11%) | | 1 (5%) |
| Renal, hyperplasia, lymphoid | | | | 1 (5%) |
| Lymph node, mandibular | (49) | (50) | (50) | (50) |
| Atrophy | 1 (2%) | | | |
| Congestion | | 1 (2%) | 1 (2%) | |
| Ectasia | 3 (6%) | 4 (8%) | 9 (18%) | 2 (4%) |
| Edema | | | | 1 (2%) |
| Hyperplasia, lymphoid | 1 (2%) | 1 (2%) | | 1 (2%) |
| Hyperplasia, plasma cell | 1 (2%) | | | |
| Infiltration cellular, plasma cell | | 1 (2%) | | |
| Necrosis | | | 1 (2%) | |
| Lymph node, mesenteric | (49) | (50) | (50) | (50) |
| Congestion | 2 (4%) | | 3 (6%) | |
| Ectasia | | | 4 (8%) | |
| Hemorrhage | 1 (2%) | | | |
| Hyperplasia, lymphoid | | 2 (4%) | | 2 (4%) |
| Inflammation, acute | | | | 1 (2%) |
| Inflammation, chronic | | | | 1 (2%) |
| Spleen | (50) | (50) | (50) | (50) |
| Atrophy | | | | 1 (2%) |
| Congestion | 1 (2%) | | 2 (4%) | |
| Fibrosis | 2 (4%) | 3 (6%) | 3 (6%) | 4 (8%) |
| Hematopoietic cell proliferation | 2 (4%) | 4 (8%) | | 2 (4%) |
| Hemorrhage | | 2 (4%) | | |
| Metaplasia, osseous | | 1 (2%) | | |
| Necrosis | | 1 (2%) | 2 (4%) | 1 (2%) |
| Pigmentation | | | | 1 (2%) |
| Capsule, inflammation, chronic | | | | 1 (2%) |
| Thymus | (50) | (50) | (50) | (50) |
| Congestion | | | 1 (2%) | |
| Cyst | | | 1 (2%) | |
| Ectopic parathyroid gland | 2 (4%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Fibrosis | | 1 (2%) | | |
| Inflammation, acute | 1 (2%) | | | |
| Inflammation, chronic | | | | 1 (2%) |

TABLE B5

Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|----------|----------|
| Integumentary System | | | | |
| Mammary gland | (50) | (50) | (50) | (50) |
| Galactocele | 3 (6%) | 5 (10%) | 1 (2%) | |
| Hyperplasia | 5 (10%) | 2 (4%) | 6 (12%) | 5 (10%) |
| Inflammation, chronic active | | | 1 (2%) | |
| Duct, dilatation | 13 (26%) | 9 (18%) | 13 (26%) | 13 (26%) |
| Skin | (50) | (50) | (50) | (50) |
| Hyperkeratosis | | | 2 (4%) | |
| Hyperplasia, squamous | 2 (4%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Inflammation, acute | 1 (2%) | | | 1 (2%) |
| Inflammation, chronic | 1 (2%) | | | |
| Inflammation, chronic active | 2 (4%) | 1 (2%) | | 1 (2%) |
| Subcutaneous tissue, fibrosis | | 1 (2%) | | |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Osteopetrosis | 9 (18%) | 12 (24%) | 10 (20%) | 5 (10%) |
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Hemorrhage | 1 (2%) | 1 (2%) | | 2 (4%) |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Congestion | 1 (2%) | | | |
| Hemorrhage | | | | 1 (2%) |
| Infiltration cellular, histiocyte | 13 (26%) | 10 (20%) | 9 (18%) | 11 (22%) |
| Inflammation, chronic | 9 (18%) | 8 (16%) | 6 (12%) | 8 (16%) |
| Bronchiole, alveolus, hyperplasia | | | 1 (2%) | |
| Nose | (50) | (50) | (50) | (50) |
| Congestion | | | 1 (2%) | |
| Cyst | 1 (2%) | 1 (2%) | | |
| Hemorrhage | | | | 1 (2%) |
| Inflammation, chronic | 2 (4%) | | 3 (6%) | |
| Inflammation, chronic active | 15 (30%) | 15 (30%) | 16 (32%) | 19 (38%) |
| Nasolacrimal duct, cyst | | 2 (4%) | | |
| Nasolacrimal duct, inflammation, chronic active | 1 (2%) | | 1 (2%) | |
| Respiratory epithelium, hyperplasia | | | | 1 (2%) |
| Special Senses System | | | | |
| Eye | | | (1) | (2) |
| Hemorrhage | | | 1 (100%) | 2 (100%) |
| Harderian gland | (1) | | | |
| Inflammation, chronic | 1 (100%) | | | |

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|-------------------------------|----------|----------|----------|----------|
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Accumulation, hyaline droplet | | | | 1 (2%) |
| Congestion | 2 (4%) | | 1 (2%) | |
| Cyst | | | 1 (2%) | |
| Hydronephrosis | | 2 (4%) | | |
| Inflammation, acute | | | | 1 (2%) |
| Mineralization | 3 (6%) | | 4 (8%) | 6 (12%) |
| Nephropathy | 41 (82%) | 42 (84%) | 35 (70%) | 37 (74%) |
| Pigmentation | | | 2 (4%) | 1 (2%) |
| Renal tubule, hyperplasia | | | | 1 (2%) |
| Urinary bladder | (50) | (50) | (50) | (50) |
| Hemorrhage | | 1 (2%) | | |
| Inflammation, chronic | | 3 (6%) | 1 (2%) | 2 (4%) |

APPENDIX C

SUMMARY OF LESIONS IN MALE WISTAR RATS IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

| | | |
|----------|---|-----|
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TABLE C1

Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine^a

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|---------|---------|----------|---------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 2 | 9 | 9 | 10 |
| Natural deaths | 26 | 27 | 30 | 33 |
| Survivors | | | | |
| Terminal sacrifice | 22 | 14 | 11 | 7 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| Alimentary System | | | | |
| Intestine large, cecum | (32) | (37) | (29) | (27) |
| Carcinoma | 1 (3%) | | | |
| Intestine small, duodenum | (39) | (44) | (42) | (42) |
| Carcinoma | | 1 (2%) | | |
| Intestine small, jejunum | (37) | (36) | (34) | (35) |
| Carcinoma | 1 (3%) | 2 (6%) | | |
| Intestine small, ileum | (28) | (32) | (28) | (31) |
| Liver | (50) | (50) | (50) | (50) |
| Cholangiocarcinoma | 1 (2%) | | | 2 (4%) |
| Hepatocellular adenoma | 2 (4%) | | 1 (2%) | |
| Histiocytic sarcoma | | | | 1 (2%) |
| Oral mucosa | (5) | (1) | (1) | |
| Squamous cell carcinoma | 1 (20%) | | | |
| Pancreas | (46) | (50) | (50) | (49) |
| Carcinoma | | 1 (2%) | | |
| Acinus, adenoma | 6 (13%) | 7 (14%) | 8 (16%) | 7 (14%) |
| Acinus, adenoma, multiple | 8 (17%) | 4 (8%) | 4 (8%) | |
| Acinus, carcinoma | 2 (4%) | | 2 (4%) | |
| Acinus, carcinoma, multiple | 2 (4%) | | 1 (2%) | |
| Stomach, forestomach | (49) | (50) | (50) | (49) |
| Fibrosarcoma | | | 1 (2%) | |
| Squamous cell papilloma | | | | 1 (2%) |
| Stomach, glandular | (49) | (50) | (48) | (48) |
| Fibrosarcoma, metastatic, stomach, forestomach | | | 1 (2%) | |
| Tongue | | | (1) | |
| Squamous cell carcinoma | | | 1 (100%) | |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Endocardium, schwannoma benign | 2 (4%) | 2 (4%) | | 1 (2%) |
| Endocrine System | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Adenoma | | 1 (2%) | | |
| Carcinoma | | | | 1 (2%) |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Pheochromocytoma malignant | 1 (2%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Pheochromocytoma benign | 5 (10%) | 4 (8%) | 1 (2%) | |

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---------------------------------------|----------|----------|----------|----------|
| Endocrine System (continued) | | | | |
| Islets, pancreatic | (47) | (50) | (49) | (49) |
| Adenoma | 8 (17%) | | 3 (6%) | |
| Carcinoma | | 1 (2%) | | 1 (2%) |
| Parathyroid gland | (48) | (47) | (48) | (47) |
| Adenoma | 1 (2%) | | | |
| Pituitary gland | (49) | (49) | (50) | (50) |
| Pars distalis, adenoma | 15 (31%) | 16 (33%) | 12 (24%) | 13 (26%) |
| Pars distalis, adenoma, multiple | 1 (2%) | 1 (2%) | | |
| Pars intermedia, adenoma | 1 (2%) | | | 1 (2%) |
| Thyroid gland | (49) | (50) | (48) | (49) |
| Bilateral, follicular cell, adenoma | | | 1 (2%) | |
| C-cell, adenoma | 4 (8%) | 2 (4%) | | 3 (6%) |
| Follicular cell, adenoma | | | 4 (8%) | |
| Follicular cell, carcinoma | 3 (6%) | 3 (6%) | 1 (2%) | |
| General Body System | | | | |
| Tissue NOS | | (1) | | |
| Hemangiosarcoma | | 1 (100%) | | |
| Genital System | | | | |
| Epididymis | (50) | (49) | (49) | (50) |
| Preputial gland | (50) | (48) | (50) | (50) |
| Adenoma | 1 (2%) | | 1 (2%) | 1 (2%) |
| Prostate | (50) | (49) | (50) | (50) |
| Adenoma | 3 (6%) | 1 (2%) | 1 (2%) | |
| Schwannoma malignant | | | | 1 (2%) |
| Seminal vesicle | (49) | (49) | (50) | (49) |
| Testes | (50) | (49) | (49) | (50) |
| Bilateral, interstitial cell, adenoma | 3 (6%) | 1 (2%) | 1 (2%) | 5 (10%) |
| Interstitial cell, adenoma | 2 (4%) | 5 (10%) | 3 (6%) | 7 (14%) |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | | | 1 (2%) |
| Lymph node | (31) | (44) | (38) | (32) |
| Iliac, hemangiosarcoma | | 1 (2%) | | |
| Pancreatic, histiocytic sarcoma | | | | 1 (3%) |
| Lymph node, mandibular | (48) | (49) | (47) | (48) |
| Histiocytic sarcoma | | | | 1 (2%) |
| Lymph node, mesenteric | (46) | (50) | (50) | (50) |
| Hemangioma | | | | 1 (2%) |
| Hemangiosarcoma | | 1 (2%) | 1 (2%) | |
| Histiocytic sarcoma | | | | 1 (2%) |
| Spleen | (49) | (50) | (49) | (49) |
| Hemangiosarcoma | | 1 (2%) | | |
| Thymus | (48) | (49) | (49) | (50) |
| Thymoma benign | 1 (2%) | | 2 (4%) | |
| Thymoma malignant | 1 (2%) | | | |

TABLE C1

Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|----------|---------|----------|----------|
| Integumentary System | | | | |
| Mammary gland | (48) | (46) | (44) | (46) |
| Carcinoma | | | 1 (2%) | |
| Fibroadenoma | 1 (2%) | 1 (2%) | | 1 (2%) |
| Skin | (50) | (50) | (50) | (50) |
| Basal cell adenoma | | 1 (2%) | | |
| Basal cell carcinoma | | | | 1 (2%) |
| Carcinoma, metastatic, Zymbal's gland | | | 1 (2%) | |
| Fibroma | | | 2 (4%) | |
| Keratoacanthoma | 7 (14%) | 3 (6%) | 2 (4%) | 1 (2%) |
| Squamous cell carcinoma | | 1 (2%) | | |
| Squamous cell papilloma | 2 (4%) | 1 (2%) | 1 (2%) | |
| Sebaceous gland, adenoma | | | 1 (2%) | |
| Subcutaneous tissue, fibroma | 5 (10%) | 6 (12%) | | 1 (2%) |
| Subcutaneous tissue, fibroma, multiple | | | | 1 (2%) |
| Subcutaneous tissue, fibrosarcoma | | | 1 (2%) | 1 (2%) |
| Subcutaneous tissue, sarcoma | 1 (2%) | | | |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Cranium, osteoma | 1 (2%) | | | |
| Joint, sarcoma | | | | 1 (2%) |
| Skeletal muscle | (1) | | (2) | |
| Fibroma | | | 1 (50%) | |
| Lipoma | 1 (100%) | | 1 (50%) | |
| Nervous System | | | | |
| Brain | (50) | (49) | (50) | (50) |
| Astrocytoma malignant | 1 (2%) | 1 (2%) | 1 (2%) | |
| Hemangioma | 1 (2%) | | | |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar carcinoma | | | 1 (2%) | |
| Carcinoma, metastatic, Zymbal's gland | | | 1 (2%) | 1 (2%) |
| Fibrosarcoma, metastatic, skin | | | | 1 (2%) |
| Histiocytic sarcoma | | | | 1 (2%) |
| Nose | (50) | (50) | (50) | (50) |
| Chondroma | | | | 1 (2%) |
| Squamous cell carcinoma, metastatic, oral mucosa | 1 (2%) | | | |
| Special Senses System | | | | |
| Zymbal's gland | (1) | | (2) | (3) |
| Carcinoma | 1 (100%) | | 2 (100%) | 3 (100%) |

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|--------|---------|---------|---------|
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (2%) | |
| Histiocytic sarcoma | | | | 1 (2%) |
| Lipoma | 1 (2%) | | | |
| Renal tubule, adenoma | 1 (2%) | 4 (8%) | 1 (2%) | 2 (4%) |
| Renal tubule, adenoma, multiple | 1 (2%) | 1 (2%) | | |
| Renal tubule, carcinoma | | | | 1 (2%) |
| Systemic Lesions | | | | |
| Multiple organs ^b | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | | | 1 (2%) |
| Leukemia mononuclear | 1 (2%) | 1 (2%) | 2 (4%) | |
| Lymphoma malignant | | 2 (4%) | | 1 (2%) |
| Mesothelioma malignant | | | 1 (2%) | |
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^c | 43 | 38 | 32 | 39 |
| Total primary neoplasms | 101 | 79 | 68 | 62 |
| Total animals with benign neoplasms | 40 | 37 | 29 | 33 |
| Total benign neoplasms | 84 | 61 | 51 | 47 |
| Total animals with malignant neoplasms | 17 | 14 | 12 | 13 |
| Total malignant neoplasms | 17 | 18 | 17 | 15 |
| Total animals with metastatic neoplasms | 1 | | 3 | 2 |
| Total metastatic neoplasms | 1 | | 4 | 2 |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

| Number of Days on Study | 2 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 |
|----------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 8 | 6 | 3 | 5 | 5 | 7 | 7 | 8 | 8 | 9 | 9 | 0 | 1 | 1 | 2 | 3 | 4 | 4 | 5 | 6 | 7 | 7 | 8 | 9 | 0 | |
| | 3 | 8 | 6 | 7 | 9 | 2 | 6 | 7 | 9 | 2 | 8 | 1 | 6 | 8 | 4 | 9 | 4 | 4 | 4 | 0 | 4 | 6 | 1 | 5 | 1 | |
| Carcass ID Number | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 3 | 1 | 5 | 0 | 4 | 4 | 3 | 4 | 0 | 3 | 2 | 1 | 2 | 3 | 4 | 3 | 2 | 4 | 0 | 2 | 4 | 0 | 3 | 3 | 2 | |
| | 6 | 3 | 0 | 3 | 7 | 1 | 1 | 3 | 1 | 8 | 8 | 4 | 4 | 2 | 6 | 0 | 3 | 8 | 5 | 7 | 4 | 7 | 9 | 5 | 6 | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, colon | A | + | A | A | A | + | + | A | + | + | + | A | A | + | + | A | A | A | A | + | + | + | + | A | + | |
| Intestine large, rectum | A | + | + | A | + | + | + | A | + | + | + | A | A | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, cecum | A | + | A | A | A | A | + | A | + | A | + | A | A | + | A | A | A | A | A | + | + | + | + | A | + | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, duodenum | A | + | + | A | A | + | + | A | + | + | + | A | A | + | + | + | A | A | + | + | + | + | + | A | + | |
| Intestine small, jejunum | A | + | + | A | A | + | + | + | + | + | + | A | A | A | + | A | A | A | + | + | + | + | + | A | + | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, ileum | A | + | + | A | A | A | + | A | A | A | A | A | A | A | + | A | A | A | A | A | A | + | A | A | + | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Cholangiocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Mesentery | | + | | | | | | | | | | | + | | | | | | | | | | | + | + | |
| Oral mucosa | | | | | | | | | + | | | | | | | | | | + | | | | | | + | |
| Squamous cell carcinoma | | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | A | + | + | + | + | + | + | + | + | |
| Acinus, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Acinus, adenoma, multiple | | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Acinus, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Acinus, carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Stomach, forestomach | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | | + | | + | + | | + | | | | | + | | + | | | | | | | | | | + | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Endocardium, schwannoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Pheochromocytoma malignant | | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | A | + | + | + | + | + | + | + | + | |
| Adenoma | | | | | | | | | | | | | | | | X | | | | | | X | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | |
| Pars distalis, adenoma | | X | | | X | | | | | | | | X | | | | | X | | | X | X | X | | | |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pars intermedia, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--------------------|---|
| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
| Number of Days on Study | 0 | 0 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | 5 | 7 | 7 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| Carcass ID Number | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Total | |
| | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 3 | 3 | 4 | 4 | 4 | Tissues/ Tumors | |
| | 5 | 1 | 9 | 2 | 4 | 6 | 8 | 9 | 0 | 1 | 2 | 5 | 6 | 7 | 8 | 0 | 2 | 9 | 3 | 4 | 7 | 0 | 2 | 5 | 9 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Harderian gland | + | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Lipoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Renal tubule, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Urinary bladder | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiples rgans | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Leukemia mononuclear | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-------|--------------------|
| | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
| Number of Days on Study | 7 | 8 | 8 | 8 | 9 | 0 | 1 | 2 | 2 | 3 | 5 | 6 | 7 | 8 | 8 | 8 | 8 | 0 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | 4 | 0 | 2 | 7 | 5 | 6 | 6 | 7 | 9 | 1 | 8 | 0 | 4 | 2 | 3 | 5 | 7 | 9 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Total | |
| Carcass ID Number | 0 | 9 | 9 | 5 | 5 | 5 | 7 | 9 | 8 | 7 | 9 | 9 | 6 | 6 | 8 | 6 | 7 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 7 | 9 | Tissues/ Tumors |
| | 0 | 3 | 4 | 2 | 7 | 9 | 7 | 6 | 5 | 5 | 0 | 1 | 2 | 3 | 7 | 8 | 4 | 1 | 3 | 5 | 6 | 0 | 7 | 3 | 8 | | |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Lymph node | + | + | | | | | + | | | | | + | + | + | | + | + | + | | | + | + | | + | + | 32 | |
| Pancreatic, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Lymph node, mandibular | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Hemangioma | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | M | + | + | + | + | + | + | | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | 46 | |
| Fibroadenoma | | | | | | | | | | X | | | | | | | | | | | | | | | | 1 | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Basal cell carcinoma | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 | |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 | |
| Subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | | X | | | | | 1 | |
| Subcutaneous tissue, fibroma, multiple | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 | |
| Subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 | |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Joint, sarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 | |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Peripheral nerve | | | + | | | | | | | + | | | | | | | | | | | | + | | | | 5 | |
| Spinal cord | | | + | | | | | | | + | | | | | | | | | | | | + | | | | 4 | |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Carcinoma, metastatic, Zymbal's gland | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 | |
| Fibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Chondroma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Harderian gland | | | | | | | | | | | | | | | + | | | | | | | | | | | 1 | |
| Zymbal's gland | | | | | | | | | | | | | | | + | | + | | | | | | | | | 3 | |
| Carcinoma | | | | | | | | | | | | | | | X | | X | | | | | | | | | 3 | |

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

[illegible]

TABLE C3

Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|-------------|-------------|-------------|----------------|
| Adrenal Medulla: Benign Pheochromocytoma | | | | |
| Overall rate ^a | 5/50 (10%) | 4/50 (8%) | 1/50 (2%) | 0/50 (0%) |
| Adjusted rate ^b | 12.5% | 11.1% | 3.0% | 0.0% |
| Terminal rate ^c | 5/22 (23%) | 2/14 (14%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 722 (T) | 486 | 721 | — ^e |
| Poly-3 test ^d | P=0.022N | P=0.568N | P=0.144N | P=0.073N |
| Adrenal Medulla: Benign or Malignant Pheochromocytoma | | | | |
| Overall rate | 6/50 (12%) | 5/50 (10%) | 2/50 (4%) | 1/50 (2%) |
| Adjusted rate | 14.8% | 13.8% | 5.8% | 3.5% |
| Terminal rate | 5/22 (23%) | 2/14 (14%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 587 | 486 | 481 | 553 |
| Poly-3 test | P=0.055N | P=0.582N | P=0.189N | P=0.133N |
| Small Intestine (Duodenum, Jejunum): Carcinoma | | | | |
| Overall rate | 1/50 (2%) | 3/50 (6%) | 0/50 (0%) | 0/50 (0%) |
| Adjusted rate | 2.5% | 8.5% | 0.0% | 0.0% |
| Terminal rate | 1/22 (5%) | 2/14 (14%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 722 (T) | 698 | — | — |
| Poly-3 test | P=0.221N | P=0.259 | P=0.534N | P=0.569N |
| Kidney (Renal Tubule): Adenoma (Single Sections) | | | | |
| Overall rate | 2/50 (4%) | 5/50 (10%) | 1/50 (2%) | 2/50 (4%) |
| Adjusted rate | 4.9% | 13.9% | 3.0% | 7.0% |
| Terminal rate | 0/22 (0%) | 1/14 (7%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 576 | 610 | 721 | 606 |
| Poly-3 test | P=0.531N | P=0.167 | P=0.564N | P=0.562 |
| Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections) | | | | |
| Overall rate | 2/50 (4%) | 5/50 (10%) | 1/50 (2%) | 3/50 (6%) |
| Adjusted rate | 4.9% | 13.9% | 3.0% | 10.4% |
| Terminal rate | 0/22 (0%) | 1/14 (7%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 576 | 610 | 721 | 606 |
| Poly-3 test | P=0.420 | P=0.167 | P=0.564N | P=0.348 |
| Kidney (Renal Tubule): Adenoma (Single and Step Sections) | | | | |
| Overall rate | 3/50 (6%) | 6/50 (12%) | 5/50 (10%) | 4/50 (8%) |
| Adjusted rate | 7.4% | 16.5% | 14.4% | 13.6% |
| Terminal rate | 1/22 (5%) | 1/14 (7%) | 2/11 (18%) | 0/7 (0%) |
| First incidence (days) | 576 | 610 | 520 | 550 |
| Poly-3 test | P=0.288 | P=0.187 | P=0.271 | P=0.328 |
| Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections) | | | | |
| Overall rate | 3/50 (6%) | 6/50 (12%) | 6/50 (12%) | 4/50 (8%) |
| Adjusted rate | 7.4% | 16.5% | 17.2% | 13.6% |
| Terminal rate | 1/22 (5%) | 1/14 (7%) | 2/11 (18%) | 0/7 (0%) |
| First incidence (days) | 576 | 610 | 520 | 550 |
| Poly-3 test | P=0.258 | P=0.187 | P=0.167 | P=0.328 |
| Pancreas: Adenoma | | | | |
| Overall rate | 14/46 (30%) | 11/50 (22%) | 12/50 (24%) | 7/49 (14%) |
| Adjusted rate | 37.4% | 28.3% | 32.9% | 23.7% |
| Terminal rate | 13/22 (59%) | 4/14 (29%) | 4/11 (36%) | 3/7 (43%) |
| First incidence (days) | 589 | 372 | 486 | 545 |
| Poly-3 test | P=0.176N | P=0.267N | P=0.433N | P=0.168N |

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|-------------|-------------|-------------|-------------|
| Pancreas: Carcinoma | | | | |
| Overall rate | 4/46 (9%) | 1/50 (2%) | 3/50 (6%) | 0/49 (0%) |
| Adjusted rate | 10.8% | 2.8% | 8.9% | 0.0% |
| Terminal rate | 4/22 (18%) | 0/14 (0%) | 3/11 (27%) | 0/7 (0%) |
| First incidence (days) | 722 (T) | 638 | 722 (T) | — |
| Poly-3 test | P=0.107N | P=0.190N | P=0.550N | P=0.105N |
| Pancreas: Adenoma or Carcinoma | | | | |
| Overall rate | 16/46 (35%) | 11/50 (22%) | 13/50 (26%) | 7/49 (14%) |
| Adjusted rate | 42.7% | 28.3% | 35.6% | 23.7% |
| Terminal rate | 15/22 (68%) | 4/14 (29%) | 5/11 (45%) | 3/7 (43%) |
| First incidence (days) | 589 | 372 | 486 | 545 |
| Poly-3 test | P=0.098N | P=0.131N | P=0.343N | P=0.077N |
| Pancreatic Islets: Adenoma | | | | |
| Overall rate | 8/47 (17%) | 0/50 (0%) | 3/49 (6%) | 0/49 (0%) |
| Adjusted rate | 20.8% | 0.0% | 8.8% | 0.0% |
| Terminal rate | 5/22 (23%) | 0/14 (0%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 624 | — | 510 | — |
| Poly-3 test | P=0.005N | P=0.005N | P=0.134N | P=0.014N |
| Pancreatic Islets: Adenoma or Carcinoma | | | | |
| Overall rate | 8/47 (17%) | 1/50 (2%) | 3/49 (6%) | 1/49 (2%) |
| Adjusted rate | 20.8% | 2.8% | 8.8% | 3.6% |
| Terminal rate | 5/22 (23%) | 0/14 (0%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 624 | 638 | 510 | 631 |
| Poly-3 test | P=0.025N | P=0.020N | P=0.134N | P=0.048N |
| Pituitary Gland (Pars Distalis): Adenoma | | | | |
| Overall rate | 16/49 (33%) | 17/49 (35%) | 12/50 (24%) | 13/50 (26%) |
| Adjusted rate | 38.2% | 45.7% | 33.1% | 39.7% |
| Terminal rate | 9/22 (41%) | 5/14 (36%) | 4/11 (36%) | 2/7 (29%) |
| First incidence (days) | 468 | 506 | 494 | 483 |
| Poly-3 test | P=0.480N | P=0.324 | P=0.404N | P=0.545 |
| Prostate Gland: Adenoma | | | | |
| Overall rate | 3/50 (6%) | 1/49 (2%) | 1/50 (2%) | 0/50 (0%) |
| Adjusted rate | 7.5% | 2.9% | 3.0% | 0.0% |
| Terminal rate | 3/22 (14%) | 1/14 (7%) | 1/11 (9%) | 0/7 (0%) |
| First incidence (days) | 722 (T) | 722 (T) | 722 (T) | — |
| Poly-3 test | P=0.097N | P=0.363N | P=0.368N | P=0.195N |
| Skin: Keratoacanthoma | | | | |
| Overall rate | 7/50 (14%) | 3/50 (6%) | 2/50 (4%) | 1/50 (2%) |
| Adjusted rate | 17.2% | 8.5% | 5.9% | 3.5% |
| Terminal rate | 4/22 (18%) | 2/14 (14%) | 1/11 (9%) | 0/7 (0%) |
| First incidence (days) | 598 | 639 | 705 | 687 |
| Poly-3 test | P=0.035N | P=0.216N | P=0.128N | P=0.090N |
| Skin: Squamous Cell Papilloma or Keratoacanthoma | | | | |
| Overall rate | 9/50 (18%) | 4/50 (8%) | 3/50 (6%) | 1/50 (2%) |
| Adjusted rate | 21.8% | 11.3% | 8.7% | 3.5% |
| Terminal rate | 5/22 (23%) | 3/14 (21%) | 1/11 (9%) | 0/7 (0%) |
| First incidence (days) | 576 | 639 | 548 | 687 |
| Poly-3 test | P=0.014N | P=0.177N | P=0.106N | P=0.038N |

TABLE C3

Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|------------|----------------|------------|-------------|
| Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma | | | | |
| Overall rate | 9/50 (18%) | 5/50 (10%) | 3/50 (6%) | 1/50 (2%) |
| Adjusted rate | 21.8% | 14.1% | 8.7% | 3.5% |
| Terminal rate | 5/22 (23%) | 4/14 (29%) | 1/11 (9%) | 0/7 (0%) |
| First incidence (days) | 576 | 639 | 548 | 687 |
| Poly-3 test | P=0.013N | P=0.282N | P=0.106N | P=0.038N |
| Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma | | | | |
| Overall rate | 9/50 (18%) | 6/50 (12%) | 3/50 (6%) | 2/50 (4%) |
| Adjusted rate | 21.8% | 17.0% | 8.7% | 7.1% |
| Terminal rate | 5/22 (23%) | 5/14 (36%) | 1/11 (9%) | 1/7 (14%) |
| First incidence (days) | 576 | 639 | 548 | 687 |
| Poly-3 test | P=0.036N | P=0.401N | P=0.106N | P=0.096N |
| Skin: Fibroma | | | | |
| Overall rate | 5/50 (10%) | 6/50 (12%) | 2/50 (4%) | 2/50 (4%) |
| Adjusted rate | 12.3% | 16.7% | 5.9% | 7.1% |
| Terminal rate | 3/22 (14%) | 4/14 (29%) | 1/11 (9%) | 2/7 (29%) |
| First incidence (days) | 572 | 552 | 683 | 722 (T) |
| Poly-3 test | P=0.198N | P=0.412 | P=0.294N | P=0.388N |
| Skin: Fibroma, Fibrosarcoma, or Sarcoma | | | | |
| Overall rate | 6/50 (12%) | 6/50 (12%) | 3/50 (6%) | 3/50 (6%) |
| Adjusted rate | 14.6% | 16.7% | 8.8% | 10.7% |
| Terminal rate | 3/22 (14%) | 4/14 (29%) | 1/11 (9%) | 2/7 (29%) |
| First incidence (days) | 572 | 552 | 674 | 709 |
| Poly-3 test | P=0.282N | P=0.527 | P=0.338N | P=0.453N |
| Testes: Adenoma | | | | |
| Overall rate | 5/50 (10%) | 6/49 (12%) | 4/49 (8%) | 12/50 (24%) |
| Adjusted rate | 12.3% | 16.9% | 11.9% | 36.6% |
| Terminal rate | 3/22 (14%) | 3/14 (21%) | 1/11 (9%) | 3/7 (43%) |
| First incidence (days) | 592 | 486 | 660 | 464 |
| Poly-3 test | P=0.008 | P=0.404 | P=0.618N | P=0.012 |
| Thyroid Gland (C-cell): Adenoma | | | | |
| Overall rate | 4/49 (8%) | 2/50 (4%) | 0/48 (0%) | 3/49 (6%) |
| Adjusted rate | 10.2% | 5.6% | 0.0% | 10.6% |
| Terminal rate | 3/22 (14%) | 1/14 (7%) | 0/11 (0%) | 1/7 (14%) |
| First incidence (days) | 701 | 581 | — | 574 |
| Poly-3 test | P=0.483N | P=0.382N | P=0.085N | P=0.634 |
| Thyroid Gland (Follicular Cell): Adenoma | | | | |
| Overall rate | 0/49 (0%) | 0/50 (0%) | 5/48 (10%) | 0/49 (0%) |
| Adjusted rate | 0.0% | 0.0% | 14.9% | 0.0% |
| Terminal rate | 0/22 (0%) | 0/14 (0%) | 1/11 (9%) | 0/7 (0%) |
| First incidence (days) | — | — ^f | 630 | — |
| Poly-3 test | P=0.220 | — ^f | P=0.019 | — |
| Thyroid Gland (Follicular Cell): Carcinoma | | | | |
| Overall rate | 3/49 (6%) | 3/50 (6%) | 1/48 (2%) | 0/49 (0%) |
| Adjusted rate | 7.6% | 8.4% | 3.0% | 0.0% |
| Terminal rate | 1/22 (5%) | 1/14 (7%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 674 | 593 | 645 | — |
| Poly-3 test | P=0.093N | P=0.618 | P=0.370N | P=0.196N |

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|-------------|-------------|-------------|-------------|
| Thyroid Gland (Follicular Cell): Adenoma or Carcinoma | | | | |
| Overall rate | 3/49 (6%) | 3/50 (6%) | 6/48 (13%) | 0/49 (0%) |
| Adjusted rate | 7.6% | 8.4% | 17.7% | 0.0% |
| Terminal rate | 1/22 (5%) | 1/14 (7%) | 1/11 (9%) | 0/7 (0%) |
| First incidence (days) | 674 | 593 | 630 | — |
| Poly-3 test | P=0.355N | P=0.618 | P=0.168 | P=0.196N |
| Zymbal's Gland: Carcinoma | | | | |
| Overall rate | 1/50 (2%) | 0/50 (0%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 2.5% | 0.0% | 5.8% | 10.3% |
| Terminal rate | 0/22 (0%) | 0/14 (0%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 660 | — | 494 | 466 |
| Poly-3 test | P=0.063 | P=0.528N | P=0.447 | P=0.200 |
| All Organs: Hemangiosarcoma | | | | |
| Overall rate | 0/50 (0%) | 3/50 (6%) | 1/50 (2%) | 0/50 (0%) |
| Adjusted rate | 0.0% | 8.5% | 3.0% | 0.0% |
| Terminal rate | 0/22 (0%) | 2/14 (14%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | — | 660 | 705 | — |
| Poly-3 test | P=0.519N | P=0.096 | P=0.466 | — |
| All Organs: Hemangioma or Hemangiosarcoma | | | | |
| Overall rate | 1/50 (2%) | 3/50 (6%) | 1/50 (2%) | 1/50 (2%) |
| Adjusted rate | 2.5% | 8.5% | 3.0% | 3.5% |
| Terminal rate | 0/22 (0%) | 2/14 (14%) | 0/11 (0%) | 0/7 (0%) |
| First incidence (days) | 705 | 660 | 705 | 631 |
| Poly-3 test | P=0.573N | P=0.259 | P=0.722 | P=0.678 |
| All Organs: Benign Neoplasms | | | | |
| Overall rate | 40/50 (80%) | 37/50 (74%) | 29/50 (58%) | 33/50 (66%) |
| Adjusted rate | 86.7% | 84.4% | 72.4% | 81.9% |
| Terminal rate | 21/22 (96%) | 13/14 (93%) | 8/11 (73%) | 6/7 (86%) |
| First incidence (days) | 468 | 372 | 486 | 464 |
| Poly-3 test | P=0.214N | P=0.497N | P=0.055N | P=0.353N |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 17/50 (34%) | 14/50 (28%) | 12/50 (24%) | 13/50 (26%) |
| Adjusted rate | 40.2% | 37.5% | 33.2% | 40.5% |
| Terminal rate | 9/22 (41%) | 7/14 (50%) | 3/11 (27%) | 2/7 (29%) |
| First incidence (days) | 587 | 552 | 481 | 466 |
| Poly-3 test | P=0.513N | P=0.496N | P=0.341N | P=0.584 |
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 43/50 (86%) | 38/50 (76%) | 32/50 (64%) | 39/50 (78%) |
| Adjusted rate | 91.2% | 86.1% | 78.4% | 90.9% |
| Terminal rate | 21/22 (96%) | 13/14 (93%) | 9/11 (82%) | 7/7 (100%) |
| First incidence (days) | 468 | 372 | 481 | 464 |
| Poly-3 test | P=0.534N | P=0.306N | P=0.050N | P=0.656N |

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pancreas, pancreatic islets, pituitary gland, prostate gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

^f Value of statistic cannot be computed.

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine^a

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|-----------------------------------|----------|----------|----------|----------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Moribund | 2 | 9 | 9 | 10 |
| Natural deaths | 26 | 27 | 30 | 33 |
| Survivors | | | | |
| Terminal sacrifice | 22 | 14 | 11 | 7 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| Alimentary System | | | | |
| Esophagus | (50) | (50) | (50) | (50) |
| Foreign body | | | 1 (2%) | 1 (2%) |
| Inflammation, acute | | | | 1 (2%) |
| Ulcer | | | | 1 (2%) |
| Muscularis, degeneration | | | | 1 (2%) |
| Intestine large, colon | (35) | (39) | (36) | (33) |
| Mineralization | | | 1 (3%) | 1 (3%) |
| Parasite metazoan | | | 1 (3%) | |
| Intestine large, rectum | (42) | (42) | (41) | (40) |
| Hemorrhage | 1 (2%) | | | |
| Mineralization | | 1 (2%) | | |
| Parasite metazoan | | | | 1 (3%) |
| Ulcer | | | | 1 (3%) |
| Intestine large, cecum | (32) | (37) | (29) | (27) |
| Congestion | | | 1 (3%) | |
| Edema | | 1 (3%) | | |
| Hemorrhage | 1 (3%) | 2 (5%) | 1 (3%) | |
| Inflammation, acute | | 2 (5%) | 2 (7%) | 1 (4%) |
| Inflammation, chronic | | | 1 (3%) | 1 (4%) |
| Ulcer | | 2 (5%) | | 2 (7%) |
| Artery, mineralization | | 1 (3%) | | |
| Intestine small, jejunum | (37) | (36) | (34) | (35) |
| Inflammation, chronic | | | | 1 (3%) |
| Liver | (50) | (50) | (50) | (50) |
| Angiectasis | 5 (10%) | 9 (18%) | 2 (4%) | |
| Basophilic focus | | | | 2 (4%) |
| Cholangiofibrosis | | | | 1 (2%) |
| Clear cell focus | 15 (30%) | 7 (14%) | 8 (16%) | 8 (16%) |
| Congestion | 19 (38%) | 12 (24%) | 6 (12%) | 17 (34%) |
| Degeneration, cystic | 7 (14%) | 13 (26%) | 9 (18%) | 5 (10%) |
| Eosinophilic focus | 14 (28%) | 12 (24%) | 4 (8%) | 2 (4%) |
| Fibrosis | 1 (2%) | 5 (10%) | 26 (52%) | 31 (62%) |
| Hemorrhage | 1 (2%) | 1 (2%) | 5 (10%) | 3 (6%) |
| Hepatodiaphragmatic nodule | 2 (4%) | 1 (2%) | 2 (4%) | |
| Hypertrophy | | | 1 (2%) | |
| Infarct | | | 1 (2%) | |
| Infiltration cellular, histiocyte | | 1 (2%) | 2 (4%) | |
| Inflammation, acute | 1 (2%) | 1 (2%) | 3 (6%) | 1 (2%) |
| Mineralization | | 1 (2%) | 3 (6%) | 3 (6%) |
| Mixed cell focus | 1 (2%) | | 1 (2%) | 1 (2%) |
| Necrosis | 6 (12%) | 7 (14%) | 6 (12%) | 2 (4%) |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C4

Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--------------------------------------|----------|----------|----------|----------|
| Alimentary System (continued) | | | | |
| Liver (continued) | (50) | (50) | (50) | (50) |
| Pigmentation | 6 (12%) | 15 (30%) | 34 (68%) | 42 (84%) |
| Regeneration | | | | 2 (4%) |
| Tension lipoidosis | | | 1 (2%) | |
| Thrombosis | | | 1 (2%) | |
| Vacuolization cytoplasmic | 18 (36%) | 18 (36%) | 12 (24%) | 15 (30%) |
| Artery, mineralization | | 1 (2%) | | |
| Bile duct, cyst | | | 2 (4%) | 3 (6%) |
| Bile duct, dilatation | | 2 (4%) | | |
| Bile duct, hyperplasia | 31 (62%) | 33 (66%) | 30 (60%) | 27 (54%) |
| Centrilobular, cytomegaly | | 1 (2%) | 1 (2%) | 1 (2%) |
| Centrilobular, degeneration | 1 (2%) | 15 (30%) | 25 (50%) | 33 (66%) |
| Centrilobular, hypertrophy | | 1 (2%) | | |
| Centrilobular, necrosis | 5 (10%) | 6 (12%) | 4 (8%) | 23 (46%) |
| Hepatocyte, atrophy | 2 (4%) | | 1 (2%) | 1 (2%) |
| Oval cell, hyperplasia | 1 (2%) | | | |
| Periportal, fibrosis | | | 5 (10%) | 7 (14%) |
| Sinusoid, congestion | 1 (2%) | | | |
| Mesentery | (7) | (1) | (2) | (2) |
| Mineralization | 1 (14%) | | | |
| Artery, inflammation | 5 (71%) | 1 (100%) | | 1 (50%) |
| Artery, mineralization | 2 (29%) | | | |
| Fat, necrosis | 1 (14%) | | | 1 (50%) |
| Vein, thrombosis | | | 2 (100%) | |
| Oral mucosa | (5) | (1) | (1) | |
| Hyperplasia, squamous | | 1 (100%) | 1 (100%) | |
| Inflammation, suppurative | 3 (60%) | | | |
| Pancreas | (46) | (50) | (50) | (49) |
| Atrophy | 2 (4%) | 3 (6%) | 3 (6%) | 1 (2%) |
| Basophilic focus | 1 (2%) | | | |
| Edema | | | 1 (2%) | |
| Fibrosis | | | 1 (2%) | |
| Hemorrhage | | 1 (2%) | | |
| Hyperplasia | 18 (39%) | 18 (36%) | 8 (16%) | 8 (16%) |
| Necrosis | 1 (2%) | | | |
| Acinus, hyperplasia | 1 (2%) | | 1 (2%) | |
| Artery, inflammation | 3 (7%) | 5 (10%) | 3 (6%) | |
| Artery, mineralization | 2 (4%) | 6 (12%) | 1 (2%) | |
| Duct, hyperplasia | 1 (2%) | 1 (2%) | 1 (2%) | |
| Salivary glands | (48) | (49) | (47) | (48) |
| Atrophy | | | | 1 (2%) |
| Inflammation, acute | | 1 (2%) | | |
| Artery, mineralization | 2 (4%) | 3 (6%) | | |
| Duct, cyst | 1 (2%) | | 1 (2%) | |

TABLE C4

Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|----------|----------|
| Alimentary System (continued) | | | | |
| Stomach, forestomach | (49) | (50) | (50) | (49) |
| Cyst | | | 1 (2%) | 2 (4%) |
| Erosion | 1 (2%) | | | |
| Fibrosis | | | | 1 (2%) |
| Foreign body | | | 1 (2%) | 2 (4%) |
| Hemorrhage | | | 1 (2%) | |
| Hyperplasia, squamous | 2 (4%) | 13 (26%) | 11 (22%) | 10 (20%) |
| Inflammation, acute | 1 (2%) | | | |
| Inflammation, chronic | | | 1 (2%) | 1 (2%) |
| Inflammation, chronic active | | | | 1 (2%) |
| Mineralization | 3 (6%) | 5 (10%) | 3 (6%) | 1 (2%) |
| Ulcer | 2 (4%) | 4 (8%) | 3 (6%) | 4 (8%) |
| Ulcer, chronic | 1 (2%) | | | |
| Stomach, glandular | (49) | (50) | (48) | (48) |
| Erosion | 3 (6%) | 3 (6%) | 2 (4%) | 4 (8%) |
| Fibrosis | | 1 (2%) | | |
| Hemorrhage | | | 2 (4%) | |
| Hyperplasia | 1 (2%) | | 1 (2%) | |
| Inflammation, chronic active | | | 1 (2%) | |
| Mineralization | 8 (16%) | 25 (50%) | 16 (33%) | 6 (13%) |
| Ulcer | | | 1 (2%) | |
| Artery, mineralization | | | 1 (2%) | 1 (2%) |
| Serosa, edema | | 1 (2%) | | |
| Tooth | (2) | (2) | (4) | (3) |
| Peridontal tissue, inflammation, chronic | | | | 1 (33%) |
| Peridontal tissue, inflammation, chronic active | 1 (50%) | | | 1 (33%) |
| Peridontal tissue, inflammation, granulomatous | | 1 (50%) | | |
| Peridontal tissue, inflammation, suppurative | 1 (50%) | 1 (50%) | 4 (100%) | 1 (33%) |
| Cardiovascular System | | | | |
| Blood vessel | (8) | (23) | (12) | (3) |
| Mineralization | 6 (75%) | 6 (26%) | 1 (8%) | |
| Aorta, mineralization | 7 (88%) | 21 (91%) | 10 (83%) | 3 (100%) |
| Pulmonary artery, degeneration | | 1 (4%) | | |
| Pulmonary artery, mineralization | 3 (38%) | 3 (13%) | 5 (42%) | 2 (67%) |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy | 49 (98%) | 49 (98%) | 49 (98%) | 47 (94%) |
| Inflammation, chronic | 1 (2%) | | | |
| Mineralization | 6 (12%) | 17 (34%) | 12 (24%) | 3 (6%) |
| Thrombosis | 1 (2%) | | 1 (2%) | |
| Artery, inflammation | | 1 (2%) | | |
| Artery, inflammation, acute | | | | 1 (2%) |
| Artery, mineralization | 4 (8%) | 15 (30%) | 9 (18%) | 2 (4%) |
| Artery, thrombosis | 1 (2%) | | | |
| Atrium, dilatation | | | 1 (2%) | 1 (2%) |
| Atrium, thrombosis | 4 (8%) | 2 (4%) | 5 (10%) | 3 (6%) |
| Valve, inflammation | | | | 1 (2%) |

TABLE C4

Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|-----------------------------------|----------|----------|----------|----------|
| Endocrine System | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Accessory adrenal cortical nodule | 1 (2%) | | | |
| Angiectasis | 1 (2%) | | 1 (2%) | |
| Congestion | | 2 (4%) | | 1 (2%) |
| Degeneration | | 2 (4%) | | |
| Hemorrhage | 3 (6%) | | | |
| Hyperplasia | 1 (2%) | 2 (4%) | 1 (2%) | 1 (2%) |
| Hypertrophy | 2 (4%) | 2 (4%) | 2 (4%) | |
| Mineralization | | 1 (2%) | | |
| Necrosis | | | | 2 (4%) |
| Thrombosis | | 1 (2%) | | 1 (2%) |
| Vacuolization cytoplasmic | 17 (34%) | 13 (26%) | 12 (24%) | 7 (14%) |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Hyperplasia | 3 (6%) | 4 (8%) | 2 (4%) | 1 (2%) |
| Islets, pancreatic | (47) | (50) | (49) | (49) |
| Hyperplasia | 1 (2%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Parathyroid gland | (48) | (47) | (48) | (47) |
| Hyperplasia | 16 (33%) | 32 (68%) | 29 (60%) | 12 (26%) |
| Inflammation, chronic | 1 (2%) | | | |
| Pituitary gland | (49) | (49) | (50) | (50) |
| Angiectasis | | | | 1 (2%) |
| Congestion | | | | 2 (4%) |
| Cyst | 17 (35%) | 13 (27%) | 18 (36%) | 11 (22%) |
| Hemorrhage | | | 1 (2%) | 1 (2%) |
| Hyperplasia | 13 (27%) | 10 (20%) | 7 (14%) | 3 (6%) |
| Hypertrophy | | | | 1 (2%) |
| Pars distalis, hyperplasia | 2 (4%) | 1 (2%) | | |
| Thyroid gland | (49) | (50) | (48) | (49) |
| Inflammation, granulomatous | | | 1 (2%) | |
| C-cell, hyperplasia | | 1 (2%) | 1 (2%) | |
| Follicle, cyst | 2 (4%) | 4 (8%) | 5 (10%) | 1 (2%) |
| Follicular cell, hyperplasia | | 2 (4%) | 1 (2%) | |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Coagulating gland | (48) | (42) | (45) | (45) |
| Inflammation, acute | | 1 (2%) | 1 (2%) | |
| Inflammation, chronic | | | | 1 (2%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Artery, mineralization | | 1 (2%) | | |
| Epididymis | (50) | (49) | (49) | (50) |
| Arteriole, mineralization | 1 (2%) | | | |
| Artery, inflammation | | | | 1 (2%) |
| Epithelium, hyperplasia | | | | 1 (2%) |

TABLE C4

Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|----------|----------|
| Genital System (continued) | | | | |
| Preputial gland | (50) | (48) | (50) | (50) |
| Atrophy | | | 1 (2%) | |
| Hyperplasia, squamous | | | | 1 (2%) |
| Inflammation, chronic | 2 (4%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Inflammation, chronic active | 1 (2%) | | 1 (2%) | |
| Inflammation, suppurative | 12 (24%) | 9 (19%) | 10 (20%) | 3 (6%) |
| Duct, cyst | 49 (98%) | 43 (90%) | 46 (92%) | 48 (96%) |
| Prostate | (50) | (49) | (50) | (50) |
| Fibrosis | | | 2 (4%) | 1 (2%) |
| Hemorrhage | 1 (2%) | | 1 (2%) | |
| Hyperplasia | 4 (8%) | 4 (8%) | 1 (2%) | 2 (4%) |
| Inflammation, acute | 4 (8%) | 1 (2%) | | |
| Inflammation, chronic | 3 (6%) | 4 (8%) | 5 (10%) | 2 (4%) |
| Inflammation, chronic active | 5 (10%) | 5 (10%) | 2 (4%) | 2 (4%) |
| Artery, mineralization | 1 (2%) | | | |
| Seminal vesicle | (49) | (49) | (50) | (49) |
| Cyst | | 1 (2%) | | |
| Hyperplasia | | 1 (2%) | | |
| Inflammation, chronic | | 1 (2%) | | |
| Inflammation, chronic active | | | 1 (2%) | |
| Artery, mineralization | | 1 (2%) | | |
| Testes | (50) | (49) | (49) | (50) |
| Atrophy | 20 (40%) | 20 (41%) | 18 (37%) | 9 (18%) |
| Congestion | | | | 1 (2%) |
| Inflammation, granulomatous | | | 1 (2%) | 1 (2%) |
| Mineralization | 6 (12%) | 2 (4%) | 9 (18%) | 4 (8%) |
| Artery, inflammation | 24 (48%) | 24 (49%) | 14 (29%) | 11 (22%) |
| Artery, mineralization | | 3 (6%) | 2 (4%) | |
| Interstitial cell, hyperplasia | 3 (6%) | 4 (8%) | 7 (14%) | 7 (14%) |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Atrophy | | 1 (2%) | | 1 (2%) |
| Erythroid cell, hyperplasia | | 1 (2%) | | |
| Myeloid cell, hyperplasia | 2 (4%) | 1 (2%) | 1 (2%) | |
| Lymph node | (31) | (44) | (38) | (32) |
| Ectasia | 2 (6%) | 1 (2%) | | |
| Hemorrhage | 2 (6%) | 1 (2%) | | |
| Hyperplasia, plasma cell | 2 (6%) | | | |
| Iliac, ectasia | 5 (16%) | 3 (7%) | 3 (8%) | 1 (3%) |
| Iliac, hemorrhage | 1 (3%) | 2 (5%) | 2 (5%) | 3 (9%) |
| Iliac, hyperplasia, lymphoid | | 1 (2%) | 2 (5%) | 1 (3%) |
| Iliac, hyperplasia, plasma cell | | 4 (9%) | 2 (5%) | 2 (6%) |
| Inguinal, atrophy | 1 (3%) | | | |
| Inguinal, ectasia | 1 (3%) | | 1 (3%) | |
| Inguinal, hemorrhage | | 1 (2%) | 1 (3%) | 1 (3%) |
| Inguinal, hyperplasia, lymphoid | | | 1 (3%) | |
| Inguinal, infiltration cellular, histiocyte | | | 1 (3%) | |

TABLE C4

Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|----------|----------|----------|----------|
| Hematopoietic System (continued) | | | | |
| Lymph node (continued) | (31) | (44) | (38) | (32) |
| Mediastinal, atrophy | | 1 (2%) | | |
| Mediastinal, congestion | 1 (3%) | 3 (7%) | 2 (5%) | 1 (3%) |
| Mediastinal, ectasia | 6 (19%) | 12 (27%) | 9 (24%) | 6 (19%) |
| Mediastinal, hemorrhage | 8 (26%) | 15 (34%) | 10 (26%) | 9 (28%) |
| Mediastinal, hyperplasia, lymphoid | | | | 1 (3%) |
| Mediastinal, hyperplasia, plasma cell | | 2 (5%) | 1 (3%) | 1 (3%) |
| Pancreatic, ectasia | 2 (6%) | 5 (11%) | | 1 (3%) |
| Pancreatic, hemorrhage | 4 (13%) | 5 (11%) | 4 (11%) | 7 (22%) |
| Pancreatic, hyperplasia, lymphoid | 2 (6%) | 1 (2%) | | 4 (13%) |
| Pancreatic, hyperplasia, plasma cell | 1 (3%) | | 2 (5%) | 2 (6%) |
| Pancreatic, pigmentation | | | 1 (3%) | |
| Renal, ectasia | 15 (48%) | 20 (45%) | 16 (42%) | 10 (31%) |
| Renal, fibrosis | | 2 (5%) | | |
| Renal, hemorrhage | 10 (32%) | 17 (39%) | 19 (50%) | 12 (38%) |
| Renal, hyperplasia, lymphoid | | | 1 (3%) | 2 (6%) |
| Renal, hyperplasia, plasma cell | | 1 (2%) | 6 (16%) | 2 (6%) |
| Renal, pigmentation | | | 3 (8%) | |
| Lymph node, mandibular | (48) | (49) | (47) | (48) |
| Congestion | | 5 (10%) | 1 (2%) | 4 (8%) |
| Ectasia | 15 (31%) | 8 (16%) | 10 (21%) | 10 (21%) |
| Hemorrhage | 3 (6%) | 1 (2%) | 3 (6%) | 1 (2%) |
| Hyperplasia, lymphoid | | 1 (2%) | | 1 (2%) |
| Hyperplasia, plasma cell | 4 (8%) | 8 (16%) | 6 (13%) | 4 (8%) |
| Lymph node, mesenteric | (46) | (50) | (50) | (50) |
| Atrophy | | 6 (12%) | 1 (2%) | 2 (4%) |
| Ectasia | 5 (11%) | 6 (12%) | 6 (12%) | 5 (10%) |
| Hemorrhage | 12 (26%) | 14 (28%) | 12 (24%) | 12 (24%) |
| Hyperplasia, lymphoid | 1 (2%) | 1 (2%) | 2 (4%) | 5 (10%) |
| Hyperplasia, plasma cell | | 2 (4%) | | 1 (2%) |
| Spleen | (49) | (50) | (49) | (49) |
| Angiectasis | 1 (2%) | | | |
| Atrophy | 2 (4%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Congestion | 1 (2%) | | 1 (2%) | |
| Fibrosis | | 1 (2%) | 1 (2%) | 1 (2%) |
| Hematopoietic cell proliferation | 1 (2%) | 2 (4%) | | 2 (4%) |
| Hyperplasia, lymphoid | 1 (2%) | | | |
| Necrosis | 1 (2%) | | | |
| Artery, mineralization | 1 (2%) | 1 (2%) | | |
| Thymus | (48) | (49) | (49) | (50) |
| Atrophy | 15 (31%) | 29 (59%) | 28 (57%) | 24 (48%) |
| Cyst | 5 (10%) | 6 (12%) | 4 (8%) | 6 (12%) |
| Ectopic parathyroid gland | 3 (6%) | 5 (10%) | 1 (2%) | 1 (2%) |
| Ectopic thyroid | 1 (2%) | | | |
| Fibrosis | | | 1 (2%) | |
| Hemorrhage | 8 (17%) | 6 (12%) | 8 (16%) | 14 (28%) |
| Hyperplasia, lymphoid | 1 (2%) | | | |
| Hyperplasia, squamous | | | | 2 (4%) |
| Artery, mineralization | | 1 (2%) | | |
| Epithelial cell, hyperplasia | | | 1 (2%) | |

TABLE C4

Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|----------|----------|----------|---------|
| Integumentary System | | | | |
| Mammary gland | (48) | (46) | (44) | (46) |
| Cyst | | 2 (4%) | | 1 (2%) |
| Hyperplasia | 4 (8%) | | 2 (5%) | 4 (9%) |
| Artery, mineralization | 3 (6%) | 5 (11%) | | |
| Duct, dilatation | 6 (13%) | 7 (15%) | 5 (11%) | 4 (9%) |
| Skin | (50) | (50) | (50) | (50) |
| Cyst | 1 (2%) | 2 (4%) | 1 (2%) | |
| Hyperkeratosis | 1 (2%) | | | |
| Hyperplasia, squamous | | 2 (4%) | 1 (2%) | 2 (4%) |
| Inflammation, chronic | 1 (2%) | 2 (4%) | | 1 (2%) |
| Inflammation, suppurative | | 1 (2%) | | 1 (2%) |
| Ulcer | 1 (2%) | 1 (2%) | | 2 (4%) |
| Hair follicle, cyst | 1 (2%) | | | 1 (2%) |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Fibrous osteodystrophy | 10 (20%) | 21 (42%) | 16 (32%) | 6 (12%) |
| Inflammation, chronic active | | 1 (2%) | | |
| Osteosclerosis | | | 1 (2%) | |
| Cartilage, degeneration | | | | 1 (2%) |
| Cranium, fibrous osteodystrophy | 10 (20%) | 15 (30%) | 13 (26%) | 2 (4%) |
| Joint, arthrosis | | | | 1 (2%) |
| Joint, fibrosis | | | | 1 (2%) |
| Joint, inflammation, chronic | | | 1 (2%) | 1 (2%) |
| Mandible, hyperplasia | | | | 1 (2%) |
| Metacarpal, inflammation, chronic active | | | | 1 (2%) |
| Metatarsal, hyperplasia | | | 1 (2%) | |
| Metatarsal, inflammation, chronic active | | | | 1 (2%) |
| Periosteum, hyperplasia | | | | 1 (2%) |
| Rib, callus | | 1 (2%) | | |
| Vertebra, fibrous osteodystrophy | | 4 (8%) | 2 (4%) | |
| Vertebra, inflammation, chronic | | | | 1 (2%) |
| Nervous System | | | | |
| Brain | (50) | (49) | (50) | (50) |
| Degeneration | | 1 (2%) | | |
| Hemorrhage | 1 (2%) | 1 (2%) | | |
| Hydrocephalus | 1 (2%) | 1 (2%) | | |
| Peripheral nerve | (1) | (4) | (2) | (5) |
| Degeneration | 1 (100%) | | | |
| Mineralization | | 2 (50%) | 2 (100%) | |
| Radicular neuropathy | | 4 (100%) | 1 (50%) | 2 (40%) |

TABLE C4

Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|--|----------|---------|----------|----------|
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Congestion | | 4 (8%) | 2 (4%) | 4 (8%) |
| Edema | | 2 (4%) | | |
| Hemorrhage | 2 (4%) | 1 (2%) | 10 (20%) | 7 (14%) |
| Inflammation, acute | 1 (2%) | 3 (6%) | | |
| Inflammation, chronic | 1 (2%) | | 1 (2%) | |
| Inflammation, granulomatous | 4 (8%) | 1 (2%) | 5 (10%) | 2 (4%) |
| Mineralization | | 1 (2%) | | |
| Necrosis | 1 (2%) | | 1 (2%) | |
| Alveolar epithelium, hyperplasia | 1 (2%) | | 2 (4%) | |
| Alveolar epithelium, hypertrophy | | 1 (2%) | | |
| Alveolus, infiltration cellular, histiocyte | 8 (16%) | 5 (10%) | 4 (8%) | |
| Alveolus, mineralization | 2 (4%) | | | |
| Artery, mineralization | 2 (4%) | 3 (6%) | | |
| Bronchus, inflammation, acute | 1 (2%) | | | |
| Bronchus, mineralization | 1 (2%) | | | |
| Interstitialium, fibrosis | 4 (8%) | 6 (12%) | 4 (8%) | 1 (2%) |
| Interstitialium, inflammation, chronic | | 2 (4%) | | |
| Nose | (50) | (50) | (50) | (50) |
| Cyst | 1 (2%) | | | |
| Erosion | 1 (2%) | | | |
| Foreign body | 11 (22%) | 4 (8%) | 6 (12%) | 1 (2%) |
| Hemorrhage | 3 (6%) | | 1 (2%) | |
| Hyperplasia, squamous | 1 (2%) | | | |
| Inflammation, acute | 7 (14%) | 7 (14%) | 4 (8%) | 2 (4%) |
| Inflammation, chronic | 7 (14%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Inflammation, chronic active | 4 (8%) | 6 (12%) | 5 (10%) | 6 (12%) |
| Metaplasia, squamous | | 1 (2%) | 1 (2%) | 2 (4%) |
| Thrombosis | | | 1 (2%) | |
| Ulcer | | | 2 (4%) | |
| Artery, thrombosis | | | | 1 (2%) |
| Olfactory epithelium, hyperplasia | 1 (2%) | | | |
| Olfactory epithelium, metaplasia | | | 1 (2%) | |
| Respiratory epithelium, hyperplasia | 20 (40%) | 9 (18%) | 12 (24%) | 15 (30%) |
| Respiratory epithelium, metaplasia | | 1 (2%) | | |
| Respiratory epithelium, metaplasia, squamous | | | 1 (2%) | |
| Trachea | (50) | (50) | (50) | (50) |
| Cyst | | 1 (2%) | | |
| Foreign body | | | 1 (2%) | |
| Inflammation, acute | | 1 (2%) | | |
| Inflammation, chronic active | | | | 1 (2%) |
| Special Senses System | | | | |
| Eye | | | (1) | |
| Cornea, ulcer | | | 1 (100%) | |
| Harderian gland | (1) | | (4) | (1) |
| Inflammation, chronic | | | | 1 (100%) |
| Lacrimal gland | | | (1) | |
| Atrophy | | | 1 (100%) | |

TABLE C4

Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 100 ppm | 200 ppm | 400 ppm |
|---|-----------|-----------|-----------|-----------|
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Congestion | 4 (8%) | | | 2 (4%) |
| Cyst | 21 (42%) | 31 (62%) | 19 (38%) | 16 (32%) |
| Hydronephrosis | 19 (38%) | 20 (40%) | 30 (60%) | 15 (30%) |
| Inflammation, acute | | 2 (4%) | | 1 (2%) |
| Mineralization | 8 (16%) | 17 (34%) | 8 (16%) | 5 (10%) |
| Nephropathy | 50 (100%) | 50 (100%) | 50 (100%) | 50 (100%) |
| Artery, mineralization | 5 (10%) | 8 (16%) | 3 (6%) | |
| Renal tubule, accumulation, hyaline droplet | | | 1 (2%) | 1 (2%) |
| Renal tubule, hyperplasia | 6 (12%) | 17 (34%) | 8 (16%) | 5 (10%) |
| Vein, thrombosis | | 2 (4%) | 1 (2%) | 3 (6%) |
| Urinary bladder | (47) | (49) | (47) | (44) |
| Dilatation | | | 1 (2%) | |
| Edema | | 1 (2%) | | |
| Hemorrhage | | | 1 (2%) | |
| Inflammation, acute | | 1 (2%) | | |
| Inflammation, chronic | 1 (2%) | | | |
| Inflammation, chronic active | | | 1 (2%) | |
| Ulcer | | 1 (2%) | | |
| Artery, mineralization | | | 1 (2%) | |
| Transitional epithelium, hyperplasia | 1 (2%) | 3 (6%) | 1 (2%) | |

APPENDIX D

SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

| | | |
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TABLE D1

Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine^a

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|---|----------|----------|----------|-----------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Accidental deaths | 2 | 1 | 1 | 3 |
| Moribund | 2 | 3 | 3 | 1 |
| Natural deaths | 11 | 18 | 11 | 11 |
| Survivors | | | | |
| Other | | | 1 | |
| Terminal sacrifice | 35 | 28 | 34 | 35 |
| Animals examined microscopically | 50 | 50 | 49 | 50 |
| Alimentary System | | | | |
| Intestine small, duodenum | (43) | (44) | (43) | (44) |
| Intestine small, jejunum | (40) | (46) | (42) | (44) |
| Carcinoma | | | | 1 (2%) |
| Histiocytic sarcoma | | | 1 (2%) | |
| Liver | (50) | (50) | (49) | (50) |
| Hemangioma | | 1 (2%) | | |
| Hemangiosarcoma | 1 (2%) | | | |
| Hemangiosarcoma, multiple | | 2 (4%) | | |
| Hepatoblastoma | 1 (2%) | 14 (28%) | 16 (33%) | 13 (26%) |
| Hepatoblastoma, multiple | 1 (2%) | 4 (8%) | 6 (12%) | 2 (4%) |
| Hepatocellular carcinoma | 12 (24%) | 16 (32%) | 15 (31%) | 22 (44%) |
| Hepatocellular carcinoma, multiple | 3 (6%) | 19 (38%) | 26 (53%) | 18 (36%) |
| Hepatocellular adenoma | 13 (26%) | 11 (22%) | 5 (10%) | 11 (22%) |
| Hepatocellular adenoma, multiple | 16 (32%) | 29 (58%) | 29 (59%) | 28 (56%) |
| Hepatocholangiocarcinoma, multiple | | 1 (2%) | | |
| Histiocytic sarcoma | 1 (2%) | 2 (4%) | | |
| Mast cell tumor malignant, metastatic, skin | | | 1 (2%) | |
| Sarcoma, metastatic, mesentery | | 1 (2%) | | |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Mesentery | (2) | (7) | (6) | (4) |
| Hepatocholangiocarcinoma, metastatic, liver | | 1 (14%) | | |
| Histiocytic sarcoma | | 1 (14%) | | |
| Sarcoma | | 1 (14%) | 1 (17%) | |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (25%) |
| Pancreas | (49) | (50) | (48) | (50) |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Stomach, forestomach | (49) | (50) | (48) | (49) |
| Squamous cell papilloma | 1 (2%) | | | |
| Stomach, glandular | (49) | (50) | (48) | (47) |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (49) | (50) |

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|--------|----------|----------|-----------|
| Endocrine System | | | | |
| Adrenal cortex | (49) | (49) | (49) | (49) |
| Adenoma | 1 (2%) | | | 1 (2%) |
| Sarcoma, metastatic, mesentery | | 1 (2%) | | |
| Capsule, adenoma | 2 (4%) | | | |
| Capsule, sarcoma, metastatic, mesentery | | | 1 (2%) | |
| Capsule, squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Adrenal medulla | (48) | (48) | (49) | (49) |
| Pheochromocytoma benign | | 1 (2%) | | |
| Sarcoma, metastatic, mesentery | | 1 (2%) | | |
| Islets, pancreatic | (49) | (50) | (48) | (50) |
| Adenoma | | 1 (2%) | 2 (4%) | 1 (2%) |
| Thyroid gland | (49) | (50) | (49) | (50) |
| Follicular cell, adenoma | 2 (4%) | 2 (4%) | 1 (2%) | 2 (4%) |
| Follicular cell, adenoma, multiple | | | 1 (2%) | |
| General Body System | | | | |
| Peritoneum | | | | (1) |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (100%) |
| Tissue NOS | | (1) | | |
| Thoracic, hemangiosarcoma | | | 1 (100%) | |
| Genital System | | | | |
| Coagulating gland | | (1) | | |
| Sarcoma, metastatic, mesentery | | 1 (100%) | | |
| Epididymis | (50) | (50) | (49) | (50) |
| Sarcoma | | 1 (2%) | | |
| Sarcoma, metastatic, mesentery | | 1 (2%) | 1 (2%) | |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Preputial gland | (50) | (50) | (49) | (49) |
| Sarcoma, metastatic, mesentery | | | 1 (2%) | |
| Prostate | (50) | (48) | (48) | (49) |
| Sarcoma, metastatic, mesentery | | | 1 (2%) | |
| Seminal vesicle | (49) | (49) | (49) | (50) |
| Sarcoma, metastatic, mesentery | | 1 (2%) | 1 (2%) | |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Testes | (50) | (50) | (49) | (50) |
| Sarcoma, metastatic, mesentery | | 1 (2%) | 1 (2%) | |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Hematopoietic System | | | | |
| Bone marrow | (49) | (50) | (49) | (50) |
| Hemangiosarcoma | | 1 (2%) | | |
| Hemangiosarcoma, metastatic, liver | | 1 (2%) | | |
| Histiocytic sarcoma | 1 (2%) | 1 (2%) | | |
| Mast cell tumor malignant, metastatic, skin | | | 1 (2%) | |

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|--------|---------|---------|-----------|
| Hematopoietic System (continued) | | | | |
| Lymph node | (2) | (4) | (4) | (2) |
| Mediastinal, hepatocholangiocarcinoma, metastatic, liver | | 1 (25%) | | |
| Mediastinal, sarcoma, metastatic, mesentery | | 1 (25%) | 1 (25%) | |
| Mediastinal, squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (50%) |
| Lymph node, mandibular | (48) | (47) | (48) | (50) |
| Mast cell tumor malignant, metastatic, skin | | | 1 (2%) | |
| Squamous cell carcinoma, metastatic, skin | 1 (2%) | | | |
| Lymph node, mesenteric | (43) | (47) | (44) | (50) |
| Hemangioma | | 1 (2%) | 1 (2%) | |
| Histiocytic sarcoma | | 1 (2%) | 1 (2%) | |
| Sarcoma, metastatic, mesentery | | | 1 (2%) | |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Spleen | (49) | (50) | (47) | (49) |
| Hemangiosarcoma | 1 (2%) | 3 (6%) | 1 (2%) | 1 (2%) |
| Hemangiosarcoma, metastatic, liver | | 1 (2%) | | |
| Histiocytic sarcoma | | 1 (2%) | | |
| Mast cell tumor malignant, metastatic, skin | | | 1 (2%) | |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Thymus | (46) | (46) | (39) | (47) |
| Hepatocellular carcinoma, metastatic, liver | | 1 (2%) | | |
| Sarcoma, metastatic, mesentery | | | 1 (3%) | |
| Integumentary System | | | | |
| Skin | (49) | (50) | (48) | (50) |
| Squamous cell carcinoma | 1 (2%) | | | |
| Subcutaneous tissue, basal cell adenoma | | | | 1 (2%) |
| Subcutaneous tissue, hemangioma | | 1 (2%) | | 1 (2%) |
| Subcutaneous tissue, hemangiosarcoma | 1 (2%) | | | |
| Subcutaneous tissue, histiocytic sarcoma | | 1 (2%) | | |
| Subcutaneous tissue, mast cell tumor malignant | | | 1 (2%) | |
| Musculoskeletal System | | | | |
| Skeletal muscle | | (3) | (2) | (1) |
| Hepatoblastoma, metastatic, liver | | 1 (33%) | | |
| Sarcoma, metastatic, mesentery | | 1 (33%) | 1 (50%) | |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (100%) |
| Nervous System | | | | |
| Brain | (50) | (50) | (49) | (50) |
| Histiocytic sarcoma | | 1 (2%) | | |

TABLE D1

Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|---|----------|---------|----------|-----------|
| Respiratory System | | | | |
| Lung | (49) | (50) | (49) | (50) |
| Alveolar/bronchiolar adenoma | 10 (20%) | 5 (10%) | 7 (14%) | 6 (12%) |
| Alveolar/bronchiolar adenoma, multiple | 2 (4%) | | 1 (2%) | 2 (4%) |
| Alveolar/bronchiolar carcinoma | 1 (2%) | 2 (4%) | 1 (2%) | 1 (2%) |
| Hemangiosarcoma, metastatic, liver | | 1 (2%) | | |
| Hepatoblastoma, metastatic, liver | | 4 (8%) | 7 (14%) | 3 (6%) |
| Hepatocellular carcinoma, metastatic, liver | 7 (14%) | 7 (14%) | 11 (22%) | 13 (26%) |
| Hepatocholangiocarcinoma, metastatic, liver | | 1 (2%) | | |
| Histiocytic sarcoma | | 1 (2%) | | |
| Mediastinum, hepatocellular carcinoma, metastatic, liver | | 1 (2%) | | |
| Mediastinum, hepatocholangiocarcinoma, metastatic, liver | | 1 (2%) | | |
| Nose | (50) | (49) | (49) | (50) |
| Special Senses System | | | | |
| Harderian gland | (5) | | | (1) |
| Adenoma | 3 (60%) | | | 1 (100%) |
| Carcinoma | 2 (40%) | | | |
| Urinary System | | | | |
| Kidney | (49) | (50) | (48) | (50) |
| Hemangiosarcoma, metastatic, tissue NOS | | | 1 (2%) | |
| Histiocytic sarcoma | | 1 (2%) | | |
| Mast cell tumor malignant, metastatic, skin | | | 1 (2%) | |
| Sarcoma, metastatic, mesentery | | | 1 (2%) | |
| Renal tubule, adenoma | | 1 (2%) | 1 (2%) | |
| Urinary bladder | (48) | (49) | (44) | (50) |
| Hemangioma | | | 1 (2%) | |
| Squamous cell carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Transitional epithelium, papilloma | 1 (2%) | | | |
| Systemic Lesions | | | | |
| Multiple organs ^b | (50) | (50) | (49) | (50) |
| Histiocytic sarcoma | 1 (2%) | 2 (4%) | 1 (2%) | |
| Lymphoma malignant | 3 (6%) | 3 (6%) | 3 (6%) | 1 (2%) |
| Mesothelioma malignant | | | 1 (2%) | 1 (2%) |

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|---|-------|---------|---------|-----------|
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^c | 43 | 49 | 48 | 47 |
| Total primary neoplasms | 79 | 122 | 122 | 114 |
| Total animals with benign neoplasms | 35 | 42 | 36 | 39 |
| Total benign neoplasms | 51 | 53 | 49 | 54 |
| Total animals with malignant neoplasms | 22 | 46 | 47 | 42 |
| Total malignant neoplasms | 28 | 69 | 73 | 60 |
| Total animals with metastatic neoplasms | 8 | 12 | 19 | 14 |
| Total metastatic neoplasms | 8 | 30 | 35 | 30 |
| Total animals with malignant neoplasms of uncertain primary site | | | | 1 |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

| Number of Days on Study | 1 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 4 | 7 | 9 | 2 | 3 | 3 | 3 | 5 | 6 | 7 | 7 | 0 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 8 | 0 | 2 | 4 | 8 | 1 | 3 | 7 | 9 | 3 | 3 | 0 | 2 | 6 | 4 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Carcass ID Number | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1 | 3 | 4 | 2 | 3 | 0 | 1 | 4 | 0 | 3 | 2 | 2 | 2 | 2 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 |
| | 2 | 7 | 0 | 5 | 2 | 5 | 7 | 3 | 1 | 0 | 7 | 1 | 3 | 4 | 4 | 1 | 3 | 4 | 5 | 6 | 8 | 9 | 0 | 2 | 6 |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | M | + | + | + | + | + | + | A | A | + | A | A | + | A | + | + | + | + | + | M | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | A | + | A | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | A | + | + | + | + | + | + | + | A | A | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | A | + | + | + | A | + | + | + | + | A | + | A | M | A | A | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | A | + | + | + | A | + | A | A | A | A | + | A | A | A | A | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | A | + | + | + | A | + | A | + | A | A | + | A | + | A | A | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatoblastoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatoblastoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | A | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Capsule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | M | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | M | + | M | + | + | + | M | + | + | + | + | + | A | M | + | M | M | M | + | + | + | M | M |
| Pituitary gland | + | + | + | + | + | + | + | + | + | M | + | + | + | + | I | A | + | + | + | + | + | + | + | M | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
|------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-----------------------------|--|
| Number of Days on Study | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| Carcass ID Number | 8 | 9 | 1 | 2 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | Total Tissues/ Tumors | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 43 | |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 | |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 43 | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 40 | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 42 | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Hepatoblastoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 | |
| Hepatoblastoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 | |
| Hepatocellular carcinoma | | | | X | X | X | X | X | X | | | | | | | | | | | | | | | X | | 12 | |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 3 | |
| Hepatocellular adenoma | X | | | | | | | | | | | | X | X | X | X | | X | | | | X | | | | 13 | |
| Hepatocellular adenoma, multiple | | | X | | X | X | | | X | | X | X | | | | | X | X | X | | | | | X | X | 16 | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Mesentery | | | | + | | | + | | | | | | | | | | | | | | | | | | | 2 | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | + | 1 | |
| Tooth | + | + | + | + | + | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 42 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Adenoma | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 | |
| Capsule, adenoma | | | | | | | | | | | | | | | X | | | | | | | | | | | 2 | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Parathyroid gland | + | M | M | + | + | + | + | M | M | + | M | + | M | + | + | + | + | M | + | + | + | + | M | + | M | 31 | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----|--|
| Number of Days on Study | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | | |
| | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | | | |
| Carcass ID Number | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | | | |
| | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 8 | 8 | 8 | 8 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 8 | 9 | 9 | | |
| | 5 | 6 | 8 | 0 | 4 | 5 | 6 | 1 | 2 | 3 | 6 | 2 | 3 | 4 | 6 | 0 | 1 | 2 | 3 | 8 | 9 | 0 | 7 | 5 | 6 | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Gallbladder | + | M | + | + | + | + | M | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | M | + | + | 33 | |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 | |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 44 | |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 44 | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 41 | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Hemangioma | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 | |
| Hemangiosarcoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| Hepatoblastoma | X | | X | | | X | | | X | | | | | X | | X | | | | | | X | | | | 14 | |
| Hepatoblastoma, multiple | | | | | | | | | | X | | | | | | | | X | | | | | | | | 4 | |
| Hepatocellular carcinoma | | | X | | | X | | | | | X | X | X | | X | X | | | | X | X | | | X | | 16 | |
| Hepatocellular carcinoma, multiple | | | X | X | X | | X | | | | X | | X | | X | | X | | X | | | X | | X | | 19 | |
| Hepatocellular adenoma | X | | | | X | | | | | X | | | X | | | X | | | | | | | X | | | 11 | |
| Hepatocellular adenoma, multiple | | X | X | X | | X | X | X | X | | X | X | | X | X | | X | X | X | X | X | X | | X | | 29 | |
| Hepatocholeangiocarcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Mesentery | | | | | | | | | | | | + | | | + | | | | | | | | + | | | 7 | |
| Hepatocholeangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | |

Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE D2

Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 2 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 |
| Number of Days on Study | 0 | 3 | 2 | 3 | 4 | 4 | 6 | 8 | 9 | 9 | 0 | 3 | 4 | 5 | 7 | 7 | 7 | 8 | 9 | 9 | 0 | 1 | 2 | 2 | 2 |
| | 8 | 7 | 2 | 2 | 6 | 9 | 1 | 7 | 1 | 5 | 8 | 8 | 5 | 0 | 4 | 6 | 7 | 0 | 2 | 6 | 2 | 5 | 2 | 2 | 2 |
| Carcass ID Number | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 7 | 7 | 6 | 6 | 9 | 8 | 7 | 7 | 9 | 8 | 5 | 5 | 8 | 7 | 8 | 5 | 6 | 6 | 6 | 7 | 6 | 8 | 5 | 5 | 5 |
| | 8 | 0 | 3 | 9 | 4 | 9 | 5 | 7 | 7 | 1 | 2 | 9 | 8 | 4 | 0 | 7 | 8 | 7 | 1 | 9 | 2 | 5 | 1 | 3 | 4 |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | X | | | | | | | | | | | | | | | | X | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma, metastatic, liver | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | X | | | | | | | | X | | | | | | X | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | X | X | | | | | X | | X | | X | |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Histiocytic sarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinum, hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | X | | | | |
| Mediastinum, hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | X | | | | | | | | | | | X | | | | | | | | | | | | |
| Lymphoma malignant | | | | | | | | | X | | | | | | | X | | | X | | X | | | | |

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--------------------|--|
| Number of Days on Study | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| Carcass ID Number | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Total | |
| | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | Tissues/ Tumors | |
| | 7 | 8 | 9 | 1 | 2 | 3 | 8 | 9 | 0 | 2 | 3 | 4 | 5 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 0 | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Penis | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Mast cell tumor malignant, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 | |
| Lymph node | | | | | | | | | + | | | | | | | | | | | | | | | | | 4 | |
| Mediastinal, sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Mast cell tumor malignant, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | M | + | M | M | + | + | + | + | + | + | + | + | + | + | + | + | 44 | |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 | |
| Mast cell tumor malignant, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Thymus | + | + | + | M | + | + | M | M | + | M | M | + | M | + | + | + | + | + | + | + | + | X | + | + | + | 39 | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | | |
| Skin | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Subcutaneous tissue, mast cell tumor malignant | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 | |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |

Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--------------------|--|
| Number of Days on Study | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
| | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | | |
| Carcass ID Number | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | Total | |
| | 7 | 7 | 7 | 7 | 7 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 9 | 9 | 9 | 9 | 9 | 0 | 6 | 6 | 6 | 9 | 9 | Tissues/ Tumors | |
| | 2 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 5 | 6 | 7 | 9 | 0 | 1 | 2 | 5 | 7 | 9 | 0 | 2 | 7 | 9 | 3 | 6 | |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | 1 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | 1 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | 1 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Urinary ladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Squamous cell carcinoma, metastatic, uncertain primary site | 1 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Lymphoma malignant | 1 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesothelioma malignant | 1 | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|-------------|----------------|--------------|--------------|
| Adrenal Cortex: Adenoma | | | | |
| Overall rate ^a | 3/49 (6%) | 0/49 (0%) | 0/49 (0%) | 1/49 (2%) |
| Adjusted rate ^b | 6.8% | 0.0% | 0.0% | 2.4% |
| Terminal rate ^c | 2/35 (6%) | 0/27 (0%) | 0/34 (0%) | 1/34 (3%) |
| First incidence (days) | 598 | — ^e | — | 722 (T) |
| Poly-3 test ^d | P=0.234N | P=0.134N | P=0.126N | P=0.321N |
| Harderian Gland: Adenoma | | | | |
| Overall rate | 3/50 (6%) | 0/50 (0%) | 0/49 (0%) | 1/50 (2%) |
| Adjusted rate | 6.7% | 0.0% | 0.0% | 2.3% |
| Terminal rate | 1/35 (3%) | 0/28 (0%) | 0/34 (0%) | 1/35 (3%) |
| First incidence (days) | 633 | — | — | 722 (T) |
| Poly-3 test | P=0.235N | P=0.133N | P=0.130N | P=0.320N |
| Harderian Gland: Adenoma or Carcinoma | | | | |
| Overall rate | 5/50 (10%) | 0/50 (0%) | 0/49 (0%) | 1/50 (2%) |
| Adjusted rate | 11.1% | 0.0% | 0.0% | 2.3% |
| Terminal rate | 3/35 (9%) | 0/28 (0%) | 0/34 (0%) | 1/35 (3%) |
| First incidence (days) | 633 | — | — | 722 (T) |
| Poly-3 test | P=0.052N | P=0.038N | P=0.036N | P=0.111N |
| Liver: Hepatocellular Adenoma | | | | |
| Overall rate | 29/50 (58%) | 40/50 (80%) | 34/49 (69%) | 39/50 (78%) |
| Adjusted rate | 63.2% | 88.0% | 75.7% | 84.9% |
| Terminal rate | 24/35 (69%) | 27/28 (96%) | 27/34 (79%) | 31/35 (89%) |
| First incidence (days) | 520 | 522 | 513 | 406 |
| Poly-3 test | P=0.031 | P=0.003 | P=0.134 | P=0.011 |
| Liver: Hepatocellular Carcinoma | | | | |
| Overall rate | 15/50 (30%) | 35/50 (70%) | 41/49 (84%) | 40/50 (80%) |
| Adjusted rate | 32.3% | 78.7% | 89.9% | 85.1% |
| Terminal rate | 9/35 (26%) | 23/28 (82%) | 32/34 (94%) | 28/35 (80%) |
| First incidence (days) | 574 | 522 | 513 | 406 |
| Poly-3 test | P<0.001 | P<0.001 | P<0.001 | P<0.001 |
| Liver: Hepatocellular Adenoma or Carcinoma | | | | |
| Overall rate | 37/50 (74%) | 45/50 (90%) | 45/49 (92%) | 47/50 (94%) |
| Adjusted rate | 78.0% | 96.5% | 96.8% | 100.0% |
| Terminal rate | 28/35 (80%) | 28/28 (100%) | 34/34 (100%) | 35/35 (100%) |
| First incidence (days) | 520 | 522 | 513 | 406 |
| Poly-3 test | P<0.001 | P=0.004 | P=0.004 | P<0.001 |
| Liver: Hepatoblastoma | | | | |
| Overall rate | 2/50 (4%) | 18/50 (36%) | 22/49 (45%) | 15/50 (30%) |
| Adjusted rate | 4.5% | 41.2% | 49.8% | 34.4% |
| Terminal rate | 2/35 (6%) | 11/28 (39%) | 17/34 (50%) | 13/35 (37%) |
| First incidence (days) | 722 (T) | 549 | 514 | 624 |
| Poly-3 test | P=0.005 | P<0.001 | P<0.001 | P<0.001 |
| Liver: Hepatocellular Carcinoma or Hepatoblastoma | | | | |
| Overall rate | 17/50 (34%) | 42/50 (84%) | 45/49 (92%) | 42/50 (84%) |
| Adjusted rate | 36.7% | 91.3% | 96.8% | 89.4% |
| Terminal rate | 11/35 (31%) | 26/28 (93%) | 34/34 (100%) | 30/35 (86%) |
| First incidence (days) | 574 | 522 | 513 | 406 |
| Poly-3 test | P<0.001 | P<0.001 | P<0.001 | P<0.001 |

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|---|-------------|--------------|--------------|--------------|
| Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma | | | | |
| Overall rate | 38/50 (76%) | 47/50 (94%) | 46/49 (94%) | 47/50 (94%) |
| Adjusted rate | 80.1% | 98.9% | 98.5% | 100.0% |
| Terminal rate | 29/35 (83%) | 28/28 (100%) | 34/34 (100%) | 35/35 (100%) |
| First incidence (days) | 520 | 522 | 513 | 406 |
| Poly-3 test | P<0.001 | P=0.002 | P=0.003 | P<0.001 |
| Lung: Alveolar/bronchiolar Adenoma | | | | |
| Overall rate | 12/49 (24%) | 5/50 (10%) | 8/49 (16%) | 8/50 (16%) |
| Adjusted rate | 27.0% | 11.9% | 18.5% | 18.3% |
| Terminal rate | 9/35 (26%) | 4/28 (14%) | 6/34 (18%) | 6/35 (17%) |
| First incidence (days) | 520 | 546 | 526 | 639 |
| Poly-3 test | P=0.303N | P=0.065N | P=0.245N | P=0.239N |
| Lung: Alveolar/bronchiolar Adenoma or Carcinoma | | | | |
| Overall rate | 13/49 (27%) | 7/50 (14%) | 9/49 (18%) | 8/50 (16%) |
| Adjusted rate | 29.1% | 16.6% | 20.8% | 18.3% |
| Terminal rate | 9/35 (26%) | 6/28 (21%) | 7/34 (21%) | 6/35 (17%) |
| First incidence (days) | 520 | 546 | 526 | 639 |
| Poly-3 test | P=0.197N | P=0.130N | P=0.258N | P=0.174N |
| Spleen: Hemangiosarcoma | | | | |
| Overall rate | 1/49 (2%) | 3/50 (6%) | 1/47 (2%) | 1/49 (2%) |
| Adjusted rate | 2.3% | 7.1% | 2.4% | 2.4% |
| Terminal rate | 1/35 (3%) | 2/28 (7%) | 1/34 (3%) | 1/35 (3%) |
| First incidence (days) | 722 (T) | 532 | 722 (T) | 722 (T) |
| Poly-3 test | P=0.459N | P=0.292 | P=0.748 | P=0.755 |
| All Organs: Hemangioma | | | | |
| Overall rate | 0/50 (0%) | 3/50 (6%) | 2/49 (4%) | 1/50 (2%) |
| Adjusted rate | 0.0% | 7.2% | 4.7% | 2.3% |
| Terminal rate | 0/35 (0%) | 1/28 (4%) | 2/34 (6%) | 1/35 (3%) |
| First incidence (days) | — | 680 | 722 (T) | 722 (T) |
| Poly-3 test | P=0.536 | P=0.107 | P=0.225 | P=0.493 |
| All Organs: Hemangiosarcoma | | | | |
| Overall rate | 2/50 (4%) | 4/50 (8%) | 2/49 (4%) | 1/50 (2%) |
| Adjusted rate | 4.5% | 9.4% | 4.7% | 2.3% |
| Terminal rate | 1/35 (3%) | 2/28 (7%) | 1/34 (3%) | 1/35 (3%) |
| First incidence (days) | 706 | 532 | 630 | 722 (T) |
| Poly-3 test | P=0.276N | P=0.313 | P=0.678 | P=0.512N |
| All Organs: Hemangioma or Hemangiosarcoma | | | | |
| Overall rate | 2/50 (4%) | 7/50 (14%) | 4/49 (8%) | 1/50 (2%) |
| Adjusted rate | 4.5% | 16.4% | 9.4% | 2.3% |
| Terminal rate | 1/35 (3%) | 3/28 (11%) | 3/34 (9%) | 1/35 (3%) |
| First incidence (days) | 706 | 532 | 630 | 722 (T) |
| Poly-3 test | P=0.215N | P=0.067 | P=0.316 | P=0.512N |
| All Organs: Malignant Lymphoma | | | | |
| Overall rate | 3/50 (6%) | 3/50 (6%) | 3/49 (6%) | 1/50 (2%) |
| Adjusted rate | 6.6% | 7.1% | 6.9% | 2.3% |
| Terminal rate | 2/35 (6%) | 0/28 (0%) | 2/34 (6%) | 1/35 (3%) |
| First incidence (days) | 542 | 595 | 226 | 722 (T) |
| Poly-3 test | P=0.233N | P=0.632 | P=0.643 | P=0.322N |

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|-------------|--------------|--------------|--------------|
| All Organs: Benign Neoplasms | | | | |
| Overall rate | 35/50 (70%) | 42/50 (84%) | 36/49 (73%) | 39/50 (78%) |
| Adjusted rate | 74.7% | 91.2% | 79.1% | 84.9% |
| Terminal rate | 27/35 (77%) | 27/28 (96%) | 28/34 (82%) | 31/35 (89%) |
| First incidence (days) | 520 | 522 | 513 | 406 |
| Poly-3 test | P=0.275 | P=0.023 | P=0.398 | P=0.157 |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 22/50 (44%) | 46/50 (92%) | 47/49 (96%) | 42/50 (84%) |
| Adjusted rate | 46.5% | 94.8% | 98.4% | 89.4% |
| Terminal rate | 13/35 (37%) | 26/28 (93%) | 34/34 (100%) | 30/35 (86%) |
| First incidence (days) | 542 | 237 | 226 | 406 |
| Poly-3 test | P<0.001 | P<0.001 | P<0.001 | P<0.001 |
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 43/50 (86%) | 49/50 (98%) | 48/49 (98%) | 47/50 (94%) |
| Adjusted rate | 88.7% | 100.0% | 100.0% | 100.0% |
| Terminal rate | 31/35 (89%) | 28/28 (100%) | 34/34 (100%) | 35/35 (100%) |
| First incidence (days) | 520 | 237 | 226 | 406 |
| Poly-3 test | P=0.009 | P=0.018 | P=0.019 | P=0.021 |

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, and spleen; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F₁ Mice^a

| | Incidence in Controls | | | |
|-------------------------------------|---------------------------|-----------------------------|----------------|---|
| | Hepatocellular Adenoma | Hepatocellular Carcinoma | Hepatoblastoma | Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma |
| Overall Historical Incidence | | | | |
| Total | 179/289 (61.9%) | 80/289 (27.7%) | 9/289 (3.1%) | 212/289 (73.4%) |
| Standard deviation | 9.1% | 11.7% | 5.0% | 11.7% |
| Range | 47%-70% | 10%-42% | 0%-12% | 53%-81% |

^a Data as of 1 August 1997

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine^a

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|----------|----------|----------|-----------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Accidental deaths | 2 | 1 | 1 | 3 |
| Moribund | 2 | 3 | 3 | 1 |
| Natural deaths | 11 | 18 | 11 | 11 |
| Survivors | | | | |
| Other | | | 1 | |
| Terminal sacrifice | 35 | 28 | 34 | 35 |
| Animals examined microscopically | 50 | 50 | 49 | 50 |
| Alimentary System | | | | |
| Gallbladder | (43) | (33) | (30) | (36) |
| Hyperplasia | | | | 1 (3%) |
| Infiltration cellular, lymphocyte | 1 (2%) | | | |
| Ulcer | | | | 1 (3%) |
| Intestine large, colon | (48) | (48) | (46) | (50) |
| Inflammation, chronic active | 1 (2%) | | | |
| Intestine large, cecum | (47) | (44) | (42) | (45) |
| Lymphoid tissue, hyperplasia | | | 2 (5%) | 1 (2%) |
| Lymphoid tissue, necrosis | | | 1 (2%) | |
| Intestine small, jejunum | (40) | (46) | (42) | (44) |
| Peyer's patch, hyperplasia, lymphoid | 1 (3%) | 1 (2%) | 3 (7%) | 1 (2%) |
| Liver | (50) | (50) | (49) | (50) |
| Angiectasis | 1 (2%) | 1 (2%) | | |
| Basophilic focus | 3 (6%) | 1 (2%) | | |
| Clear cell focus | 1 (2%) | 3 (6%) | 1 (2%) | 2 (4%) |
| Cyst | | | 1 (2%) | |
| Eosinophilic focus | 19 (38%) | 22 (44%) | 18 (37%) | 15 (30%) |
| Hematopoietic cell proliferation | | 1 (2%) | 1 (2%) | |
| Hemorrhage | 1 (2%) | | | |
| Infiltration cellular, mixed cell | 1 (2%) | 1 (2%) | | 1 (2%) |
| Mixed cell focus | 4 (8%) | 2 (4%) | 1 (2%) | 1 (2%) |
| Necrosis | 3 (6%) | 5 (10%) | 7 (14%) | 6 (12%) |
| Vacuolization cytoplasmic, diffuse | 2 (4%) | 1 (2%) | | |
| Centrilobular, congestion | 1 (2%) | | | |
| Centrilobular, hypertrophy | | | | 1 (2%) |
| Centrilobular, vacuolization cytoplasmic | 1 (2%) | 2 (4%) | | 6 (12%) |
| Periportal, vacuolization cytoplasmic | 1 (2%) | | | 2 (4%) |
| Mesentery | (2) | (7) | (6) | (4) |
| Fat, necrosis | 2 (100%) | 3 (43%) | 1 (17%) | 2 (50%) |
| Oral mucosa | (1) | | | |
| Ulcer | 1 (100%) | | | |
| Pancreas | (49) | (50) | (48) | (50) |
| Acinus, atrophy | 3 (6%) | 2 (4%) | 1 (2%) | 1 (2%) |
| Acinus, cytoplasmic alteration | | | 1 (2%) | 1 (2%) |
| Duct, cyst | | | 1 (2%) | 1 (2%) |
| Salivary glands | (48) | (50) | (49) | (50) |
| Infiltration cellular, lymphocyte | 31 (65%) | 33 (66%) | 26 (53%) | 34 (68%) |
| Stomach, forestomach | (49) | (50) | (48) | (49) |
| Inflammation, chronic | | | | 1 (2%) |
| Inflammation, chronic active | 1 (2%) | 1 (2%) | 2 (4%) | 2 (4%) |
| Ulcer | | | | 1 (2%) |
| Epithelium, hyperplasia | | 1 (2%) | 2 (4%) | 2 (4%) |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--------------------------------------|-----------|-----------|----------|-----------|
| Alimentary System (continued) | | | | |
| Stomach, glandular | (49) | (50) | (48) | (47) |
| Necrosis | 2 (4%) | 2 (4%) | 4 (8%) | 1 (2%) |
| Glands, dysplasia | | | 2 (4%) | |
| Tooth | (42) | (10) | (1) | (3) |
| Developmental malformation | 42 (100%) | 10 (100%) | 1 (100%) | 3 (100%) |
| Cardiovascular System | | | | |
| Blood vessel | (50) | (49) | (47) | (49) |
| Aorta, thrombosis | 1 (2%) | | | |
| Heart | (50) | (50) | (49) | (50) |
| Cardiomyopathy | | | 1 (2%) | |
| Mineralization | | 3 (6%) | | |
| Thrombosis | | | | 1 (2%) |
| Artery, inflammation, chronic active | 2 (4%) | | | |
| Myocardium, hypertrophy | 1 (2%) | | | |
| Endocrine System | | | | |
| Adrenal cortex | (49) | (49) | (49) | (49) |
| Cytoplasmic alteration | 18 (37%) | 13 (27%) | 9 (18%) | 11 (22%) |
| Hyperplasia | 2 (4%) | 1 (2%) | 2 (4%) | |
| Vacuolization cytoplasmic | 2 (4%) | | | 1 (2%) |
| Capsule, hyperplasia | 42 (86%) | 29 (59%) | 30 (61%) | 29 (59%) |
| Islets, pancreatic | (49) | (50) | (48) | (50) |
| Hyperplasia | | 5 (10%) | 2 (4%) | |
| Parathyroid gland | (31) | (35) | (40) | (31) |
| Cyst | 1 (3%) | 1 (3%) | | |
| Pituitary gland | (46) | (47) | (45) | (49) |
| Cyst | 1 (2%) | 1 (2%) | | |
| Pars distalis, hyperplasia | | | 1 (2%) | |
| Thyroid gland | (49) | (50) | (49) | (50) |
| Infiltration cellular, lymphocyte | | 1 (2%) | | |
| Follicle, cyst | 1 (2%) | | | |
| Follicular cell, hyperplasia | 8 (16%) | 14 (28%) | 20 (41%) | 12 (24%) |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Epididymis | (50) | (50) | (49) | (50) |
| Angiectasis | | 1 (2%) | | |
| Infiltration cellular, lymphocyte | 1 (2%) | 4 (8%) | 4 (8%) | 4 (8%) |
| Inflammation, granulomatous | 1 (2%) | 1 (2%) | | 3 (6%) |
| Penis | | | (1) | |
| Inflammation, chronic active | | | 1 (100%) | |
| Preputial gland | (50) | (50) | (49) | (49) |
| Atrophy | 48 (96%) | 45 (90%) | 47 (96%) | 42 (86%) |
| Cyst | 29 (58%) | 25 (50%) | 32 (65%) | 28 (57%) |
| Inflammation, chronic | 18 (36%) | 18 (36%) | 13 (27%) | 12 (24%) |
| Inflammation, chronic active | 4 (8%) | 6 (12%) | 3 (6%) | 6 (12%) |

TABLE D5**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine**

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|---|----------|----------|----------|-----------|
| Genital System (continued) | | | | |
| Prostate | (50) | (48) | (48) | (49) |
| Cyst | 1 (2%) | | | |
| Hyperplasia | 1 (2%) | | | 1 (2%) |
| Inflammation, chronic | 7 (14%) | 3 (6%) | 10 (21%) | 8 (16%) |
| Inflammation, chronic active | 1 (2%) | | | 1 (2%) |
| Testes | (50) | (50) | (49) | (50) |
| Atrophy | 2 (4%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Mineralization | 1 (2%) | | | |
| Interstitial cell, hyperplasia | 1 (2%) | | | |
| Hematopoietic System | | | | |
| Bone marrow | (49) | (50) | (49) | (50) |
| Atrophy | 2 (4%) | | | |
| Erythroid cell, hyperplasia | | 1 (2%) | | |
| Myeloid cell, hyperplasia | 1 (2%) | 1 (2%) | | 1 (2%) |
| Lymph node | (2) | (4) | (4) | (2) |
| Iliac, hyperplasia, lymphoid | 1 (50%) | | | |
| Mediastinal, congestion | 1 (50%) | | | |
| Pancreatic, hyperplasia, lymphoid | | 1 (25%) | | |
| Renal, hemorrhage | | | 2 (50%) | 1 (50%) |
| Renal, necrosis | | | 1 (25%) | |
| Lymph node, mandibular | (48) | (47) | (48) | (50) |
| Hyperplasia, lymphoid | 3 (6%) | | 1 (2%) | 1 (2%) |
| Hyperplasia, plasma cell | 2 (4%) | | | |
| Necrosis | | | 1 (2%) | |
| Lymph node, mesenteric | (43) | (47) | (44) | (50) |
| Angiectasis | | 2 (4%) | | |
| Atrophy | | | | 1 (2%) |
| Hematopoietic cell proliferation | 2 (5%) | 3 (6%) | 6 (14%) | 1 (2%) |
| Hemorrhage | 13 (30%) | 10 (21%) | 10 (23%) | 12 (24%) |
| Hyperplasia, histiocytic | 2 (5%) | | 1 (2%) | |
| Hyperplasia, lymphoid | 1 (2%) | 5 (11%) | 3 (7%) | 4 (8%) |
| Hyperplasia, plasma cell | 1 (2%) | 1 (2%) | | |
| Necrosis | | | 1 (2%) | |
| Spleen | (49) | (50) | (47) | (49) |
| Atrophy | | 2 (4%) | 3 (6%) | |
| Hematopoietic cell proliferation | 13 (27%) | 30 (60%) | 26 (55%) | 23 (47%) |
| Hyperplasia, lymphoid | | 1 (2%) | 1 (2%) | 1 (2%) |
| Necrosis | | | 1 (2%) | |
| Thymus | (46) | (46) | (39) | (47) |
| Atrophy | 26 (57%) | 21 (46%) | 16 (41%) | 16 (34%) |
| Cyst | | 1 (2%) | | |
| Necrosis | | | 1 (3%) | 1 (2%) |
| Integumentary System | | | | |
| Skin | (49) | (50) | (48) | (50) |
| Inflammation, chronic active | 1 (2%) | | | |
| Ulcer | 1 (2%) | | | |
| Subcutaneous tissue, edema | 1 (2%) | 1 (2%) | | |
| Subcutaneous tissue, inflammation, acute | | 1 (2%) | | |
| Subcutaneous tissue, inflammation, chronic active | 1 (2%) | 1 (2%) | | |

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|----------|----------|----------|-----------|
| Musculoskeletal System | | | | |
| None | | | | |
| Nervous System | | | | |
| Brain | (50) | (50) | (49) | (50) |
| Hemorrhage | | 1 (2%) | | |
| Inflammation, chronic active | 1 (2%) | | | |
| Mineralization | 41 (82%) | 27 (54%) | 30 (61%) | 35 (70%) |
| Peripheral nerve | | (1) | (1) | |
| Sciatic, degeneration | | 1 (100%) | | |
| Respiratory System | | | | |
| Lung | (49) | (50) | (49) | (50) |
| Congestion | 1 (2%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Hemorrhage | | 1 (2%) | | |
| Infiltration cellular, lymphocyte | | 4 (8%) | 2 (4%) | |
| Alveolar epithelium, hyperplasia | 4 (8%) | 8 (16%) | 1 (2%) | 2 (4%) |
| Alveolus, infiltration cellular, histiocyte | 1 (2%) | 2 (4%) | 4 (8%) | 1 (2%) |
| Nose | (50) | (49) | (49) | (50) |
| Foreign body | 1 (2%) | | | |
| Olfactory epithelium, degeneration, hyaline | 15 (30%) | 31 (63%) | 35 (71%) | 7 (14%) |
| Olfactory epithelium, glands, hyperplasia | 1 (2%) | | | |
| Respiratory epithelium, degeneration, hyaline | 20 (40%) | 10 (20%) | 15 (31%) | 2 (4%) |
| Respiratory epithelium, hyperplasia | 20 (40%) | 22 (45%) | 11 (22%) | 15 (30%) |
| Respiratory epithelium, inflammation, chronic active | 2 (4%) | 1 (2%) | | 1 (2%) |
| Special Senses System | | | | |
| Eye | (1) | | | (1) |
| Cataract | 1 (100%) | | | |
| Cornea, inflammation, chronic | 1 (100%) | | | |
| Cornea, inflammation, chronic active | | | | 1 (100%) |
| Urinary System | | | | |
| Kidney | (49) | (50) | (48) | (50) |
| Atrophy | | | | 1 (2%) |
| Cyst | 4 (8%) | 2 (4%) | 4 (8%) | |
| Fibrosis | | 1 (2%) | | |
| Hydronephrosis | 1 (2%) | | | |
| Infarct | 2 (4%) | 1 (2%) | 2 (4%) | 6 (12%) |
| Infiltration cellular, lymphocyte | 3 (6%) | 1 (2%) | 2 (4%) | 6 (12%) |
| Inflammation, chronic active | 2 (4%) | | | |
| Mineralization | 2 (4%) | 3 (6%) | | |
| Nephropathy | 34 (69%) | 27 (54%) | 25 (52%) | 32 (64%) |
| Artery, inflammation, chronic | 1 (2%) | | | |
| Artery, inflammation, chronic active | 1 (2%) | | | |
| Renal tubule, accumulation, hyaline droplet | | 1 (2%) | | |
| Renal tubule, dilatation | | 1 (2%) | 2 (4%) | 5 (10%) |
| Renal tubule, hyperplasia | 3 (6%) | | 1 (2%) | 1 (2%) |
| Renal tubule, pigmentation | | 5 (10%) | 3 (6%) | 2 (4%) |
| Urinary bladder | (48) | (49) | (44) | (50) |
| Infiltration cellular, lymphocyte | 8 (17%) | 7 (14%) | 9 (20%) | 8 (16%) |

APPENDIX E

SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

| | | |
|-----------------|--|------------|
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TABLE E1

Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine^a

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|--|----------|----------|----------|----------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Accidental deaths | 3 | 6 | 4 | 5 |
| Moribund | 3 | 2 | 3 | 5 |
| Natural deaths | 12 | 12 | 21 | 11 |
| Survivors | | | | |
| Terminal sacrifice | 32 | 30 | 22 | 29 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| Alimentary System | | | | |
| Esophagus | (50) | (50) | (50) | (50) |
| Gallbladder | (37) | (40) | (33) | (34) |
| Intestine large, rectum | (44) | (48) | (47) | (47) |
| Intestine large, cecum | (44) | (49) | (40) | (45) |
| Leiomyosarcoma | | | | 1 (2%) |
| Intestine small, jejunum | (42) | (47) | (38) | (43) |
| Intestine small, ileum | (43) | (48) | (37) | (41) |
| Carcinoma | | | | 1 (2%) |
| Liver | (49) | (50) | (50) | (50) |
| Hemangioma | | | | 1 (2%) |
| Hepatoblastoma | 1 (2%) | 2 (4%) | 6 (12%) | 12 (24%) |
| Hepatoblastoma, multiple | | | 3 (6%) | 4 (8%) |
| Hepatocellular carcinoma | 10 (20%) | 12 (24%) | 19 (38%) | 11 (22%) |
| Hepatocellular carcinoma, multiple | 3 (6%) | 11 (22%) | 14 (28%) | 30 (60%) |
| Hepatocellular adenoma | 13 (27%) | 5 (10%) | 6 (12%) | 4 (8%) |
| Hepatocellular adenoma, multiple | 24 (49%) | 34 (68%) | 37 (74%) | 30 (60%) |
| Histiocytic sarcoma | 1 (2%) | 1 (2%) | | |
| Sarcoma, metastatic, skin | 1 (2%) | | | |
| Mesentery | (17) | (18) | (13) | (13) |
| Hepatoblastoma, metastatic, liver | | | 1 (8%) | 1 (8%) |
| Histiocytic sarcoma | | 2 (11%) | | |
| Lipoma | | 1 (6%) | | |
| Sarcoma | | 2 (11%) | | |
| Pancreas | (49) | (49) | (47) | (48) |
| Histiocytic sarcoma | | 2 (4%) | | |
| Sarcoma, metastatic, mesentery | | 1 (2%) | | |
| Salivary glands | (50) | (50) | (49) | (50) |
| Schwannoma malignant, metastatic, skin | | 1 (2%) | | |
| Stomach, forestomach | (49) | (49) | (49) | (49) |
| Squamous cell papilloma | | 1 (2%) | | |
| Stomach, glandular | (48) | (49) | (48) | (49) |
| Cardiovascular System | | | | |
| Blood vessel | (48) | (47) | (47) | (47) |
| Aorta, histiocytic sarcoma | | 1 (2%) | | |
| Heart | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | 1 (2%) | | |
| Sarcoma, metastatic, skin | | | 1 (2%) | |

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|--|---------|----------|---------|---------|
| Endocrine System | | | | |
| Adrenal cortex | (49) | (50) | (48) | (50) |
| Carcinoma, multiple | 1 (2%) | | | |
| Histiocytic sarcoma | 1 (2%) | 1 (2%) | | |
| Sarcoma, metastatic, mesentery | | 1 (2%) | | |
| Capsule, adenoma | 1 (2%) | | | |
| Islets, pancreatic | (49) | (50) | (47) | (49) |
| Adenoma | 1 (2%) | 2 (4%) | | |
| Pituitary gland | (47) | (44) | (42) | (46) |
| Pars distalis, adenoma | 8 (17%) | 9 (20%) | 6 (14%) | 2 (4%) |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Follicular cell, adenoma | 3 (6%) | 2 (4%) | 3 (6%) | 3 (6%) |
| General Body System | | | | |
| Peritoneum | | | (2) | |
| Hepatoblastoma, metastatic, liver | | | 1 (50%) | |
| Tissue NOS | | | (2) | |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (50%) | |
| Hepatoblastoma, metastatic, liver | | | 1 (50%) | |
| Genital System | | | | |
| Clitoral gland | (47) | (48) | (48) | (45) |
| Ovary | (47) | (49) | (46) | (49) |
| Cystadenoma | 4 (9%) | 3 (6%) | 1 (2%) | |
| Granulosa cell tumor benign | 1 (2%) | | 1 (2%) | |
| Hemangioma | | | | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | 1 (2%) | | |
| Sarcoma, metastatic, mesentery | | 1 (2%) | | |
| Oviduct | | (1) | | |
| Schwannoma malignant, metastatic, skin | | 1 (100%) | | |
| Uterus | (48) | (50) | (47) | (50) |
| Adenoma | 1 (2%) | | | |
| Histiocytic sarcoma | | 1 (2%) | | |
| Polyp stromal | 2 (4%) | 1 (2%) | | |
| Hematopoietic System | | | | |
| Bone marrow | (49) | (50) | (49) | (50) |
| Histiocytic sarcoma | 1 (2%) | 1 (2%) | | |
| Lymph node | (10) | (10) | (7) | (7) |
| Iliac, histiocytic sarcoma | 1 (10%) | 1 (10%) | | |
| Iliac, rhabdomyosarcoma, metastatic, skeletal muscle | | 1 (10%) | | |
| Mediastinal, sarcoma, metastatic, mesentery | | 1 (10%) | | |
| Mediastinal, sarcoma, metastatic, skin | 1 (10%) | | | |
| Pancreatic, hepatoblastoma, metastatic, liver | | | 1 (14%) | |
| Pancreatic, sarcoma, metastatic, mesentery | | 1 (10%) | | |
| Lymph node, mandibular | (48) | (50) | (49) | (47) |
| Histiocytic sarcoma | 2 (4%) | 1 (2%) | | |
| Sarcoma, metastatic, skin | | | 1 (2%) | |
| Schwannoma malignant, metastatic, skin | | 1 (2%) | | |

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|---|--------|----------|----------|----------|
| Hematopoietic System (continued) | | | | |
| Lymph node, mesenteric | (48) | (47) | (43) | (45) |
| Hemangioma | | | | 1 (2%) |
| Hepatoblastoma, metastatic, liver | | | 1 (2%) | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | 2 (4%) | | |
| Spleen | (49) | (50) | (48) | (49) |
| Histiocytic sarcoma | 1 (2%) | 1 (2%) | | |
| Thymus | (45) | (44) | (46) | (39) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (2%) | |
| Histiocytic sarcoma | | 1 (2%) | | |
| Integumentary System | | | | |
| Skin | (49) | (50) | (50) | (50) |
| Squamous cell papilloma | 1 (2%) | 1 (2%) | | |
| Subcutaneous tissue, hemangioma | | | 1 (2%) | |
| Subcutaneous tissue, hemangiosarcoma | | | 1 (2%) | |
| Subcutaneous tissue, sarcoma | 2 (4%) | 2 (4%) | 3 (6%) | 4 (8%) |
| Subcutaneous tissue, schwannoma malignant | 1 (2%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Musculoskeletal System | | | | |
| Skeletal muscle | | (1) | (1) | (1) |
| Hepatoblastoma, metastatic, liver | | | 1 (100%) | |
| Rhabdomyosarcoma | | 1 (100%) | | |
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | 1 (2%) | 3 (6%) | | 3 (6%) |
| Alveolar/bronchiolar adenoma, multiple | 1 (2%) | | | |
| Alveolar/bronchiolar carcinoma | 2 (4%) | 1 (2%) | 2 (4%) | 3 (6%) |
| Carcinoma, metastatic, harderian gland | 1 (2%) | | | |
| Hepatoblastoma, metastatic, liver | | | 1 (2%) | 3 (6%) |
| Hepatocellular carcinoma, metastatic, liver | 2 (4%) | | 6 (12%) | 10 (20%) |
| Histiocytic sarcoma | 1 (2%) | 1 (2%) | | |
| Rhabdomyosarcoma, metastatic, skeletal muscle | | 1 (2%) | | |
| Sarcoma, metastatic, mesentery | | 1 (2%) | | |
| Sarcoma, metastatic, skin | | | 2 (4%) | |
| Schwannoma malignant, metastatic, skin | | 1 (2%) | | |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (2%) | |
| Mediastinum, sarcoma, metastatic, skin | | | 1 (2%) | |
| Mediastinum, schwannoma malignant, metastatic, skin | | 1 (2%) | | |
| Nose | (50) | (50) | (47) | (50) |
| Sarcoma | | | | 1 (2%) |
| Sarcoma, metastatic, skin | 1 (2%) | | | |
| Trachea | (50) | (50) | (50) | (50) |

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|---|----------|----------|---------|----------|
| Special Senses System | | | | |
| Harderian gland | (1) | (1) | | (1) |
| Adenoma | | 1 (100%) | | |
| Carcinoma | 1 (100%) | | | 1 (100%) |
| Urinary System | | | | |
| Kidney | (49) | (50) | (49) | (49) |
| Histiocytic sarcoma | 1 (2%) | 1 (2%) | | |
| Schwannoma malignant, metastatic, skin | | 1 (2%) | | |
| Urinary bladder | (45) | (49) | (44) | (43) |
| Histiocytic sarcoma | | 1 (2%) | | |
| Systemic Lesions | | | | |
| Multiple organs ^b | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | 2 (4%) | 2 (4%) | | |
| Leukemia granulocytic | | 1 (2%) | | |
| Lymphoma malignant | 6 (12%) | 7 (14%) | 4 (8%) | 6 (12%) |
| Mesothelioma malignant | | | | 2 (4%) |
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^c | 47 | 45 | 45 | 45 |
| Total primary neoplasms | 90 | 105 | 108 | 122 |
| Total animals with benign neoplasms | 40 | 41 | 43 | 36 |
| Total benign neoplasms | 61 | 63 | 55 | 45 |
| Total animals with malignant neoplasms | 26 | 30 | 40 | 44 |
| Total malignant neoplasms | 29 | 42 | 53 | 77 |
| Total animals with metastatic neoplasms | 5 | 3 | 10 | 12 |
| Total metastatic neoplasms | 6 | 14 | 21 | 15 |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE E2

Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

| Number of Days on Study | 0 | 1 | 3 | 4 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 | 5 | 7 | 7 | 5 | 6 | 6 | 2 | 4 | 4 | 6 | 7 | 8 | 9 | 9 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 4 | 1 | 5 | 6 | 4 | 5 | 8 | 5 | 4 | 4 | 2 | 0 | 7 | 1 | 7 | 1 | 4 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Carcass ID Number | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 6 | 2 | 5 | 3 | 3 | 4 | 4 | 2 | 5 | 5 | 1 | 2 | 4 | 4 | 5 | 2 | 5 | 6 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 4 | 7 | 8 | 5 | 0 | 8 | 4 | 6 | 0 | 3 | 7 | 8 | 5 | 7 | 6 | 4 | 7 | 3 | 6 | 8 | 9 | 0 | 1 | 2 | 3 | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | A | + | + | + | + | A | A | + | + | A | A | A | M | A | + | A | A | A | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | A | + | + | + | + | + | + | + | + | + | A | + | A | A | + | + | A | M | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | A | + | + | + | + | A | + | + | + | + | A | + | A | A | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | A | + | + | A | + | + | + | + | + | + | A | + | A | + | + | + | A | A | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | A | + | + | A | + | A | A | + | + | A | A | + | A | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | A | + | + | + | + | A | + | + | + | + | A | A | A | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + |
| Hepatoblastoma | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | X | X | | | | X | | | | X | | | | | | X | | | | | | | |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Hepatocellular adenoma | | | | | | X | X | | | | | | X | | | | | | | X | | | | | X | | X |
| Hepatocellular adenoma, multiple | | | | | X | | | X | | X | | X | | X | X | X | | | X | | | | X | | X | | X |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | + | + | + | | + | | | | + | + | + | | + | | + | | | | | | | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | A | + | + | + | + | + | + | + | + | + |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | M | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| Carcinoma, multiple | | | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Histiocytic sarcoma | | | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Capsule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | M | + | + | + | + | M | + | M | + | + | + | M | + | + | M | M | M | M | M | M | + | M | M | + | + | M | |
| Pituitary gland | + | + | + | + | M | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | | |

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | |
|-------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Days on Study | 0 | 1 | 3 | 4 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | 6 | 5 | 7 | 7 | 5 | 6 | 6 | 2 | 4 | 4 | 6 | 7 | 8 | 9 | 9 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 4 | 1 | 5 | 6 | 4 | 5 | 8 | 5 | 4 | 4 | 2 | 0 | 7 | 1 | 7 | 1 | 4 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Carcass ID Number | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 6 | 2 | 5 | 3 | 3 | 4 | 4 | 2 | 5 | 5 | 1 | 2 | 4 | 4 | 5 | 2 | 5 | 6 | 1 | 1 | 1 | 2 | 2 | 2 |
| | 4 | 7 | 8 | 5 | 0 | 8 | 4 | 6 | 0 | 3 | 7 | 8 | 5 | 7 | 6 | 4 | 7 | 3 | 6 | 8 | 9 | 0 | 1 | 2 |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | X | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | A | + | + | + | A | A | + | A | + | + | + | A | + | + | + | + | + | + | + |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | X | | | | X | | | | | | | | | | | | | | | | |
| Lymphoma malignant | | | | | | | | | | | | | | X | | X | X | X | | | | | X | |

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

| | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0 | 0 | 1 | 3 | 4 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| Number of Days on Study | 0 | 1 | 2 | 7 | 7 | 1 | 5 | 7 | 9 | 0 | 0 | 4 | 4 | 7 | 7 | 8 | 9 | 1 | 1 | 2 | 2 | 2 | 2 |
| | 4 | 6 | 0 | 2 | 2 | 9 | 5 | 3 | 9 | 5 | 8 | 2 | 9 | 4 | 7 | 0 | 6 | 1 | 3 | 4 | 9 | 9 | 9 |
| | 2 | 2 | 2 | 3 | 2 | 3 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 3 | 2 | 2 | 2 | 2 |
| Carcass ID Number | 7 | 8 | 7 | 0 | 8 | 1 | 9 | 8 | 6 | 7 | 9 | 0 | 7 | 9 | 9 | 8 | 6 | 0 | 7 | 0 | 6 | 6 | 7 |
| | 0 | 4 | 9 | 5 | 1 | 1 | 5 | 9 | 9 | 7 | 1 | 1 | 1 | 4 | 7 | 2 | 8 | 6 | 5 | 7 | 6 | 7 | 2 |
| | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | | | | | | | | X | | | | | | X |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | X | | | | | | | |
| Oviduct | | | | | | | | | | | | + | | | | | | | | | | | |
| Schwannoma malignant, metastatic, skin | | | | | | | | | | | | X | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node | | | | | | | | | | + | + | | | + | + | + | | + | | | | | + |
| Iliac, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | |
| Iliac, rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | X | | | | | | | |
| Mediastinal, sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | X | | | | | | |
| Pancreatic, sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | X | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | |
| Schwannoma malignant, metastatic, skin | | | | | | | | | | | | X | | | | | | | | | | | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | M | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | M | + | + | M | + | M | + | + | + | + | + | M | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, sarcoma | | | | | | | | | X | | | | | | | | | | | | | | X |
| Subcutaneous tissue, schwannoma malignant | | | | | | | | | | | | | X | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | | | + | | | | | | | |
| Rhabdomyosarcoma | | | | | | | | | | | | | | | | X | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

TABLE E2

Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Days on Study | 0 | 0 | 0 | 1 | 3 | 4 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | 0 | 1 | 2 | 7 | 7 | 1 | 5 | 7 | 9 | 0 | 0 | 4 | 4 | 7 | 7 | 8 | 9 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| | 4 | 6 | 0 | 2 | 2 | 9 | 5 | 3 | 9 | 5 | 8 | 2 | 9 | 4 | 7 | 0 | 6 | 1 | 3 | 4 | 9 | 9 | 9 | 9 | 9 |
| Carcass ID Number | 2 | 2 | 2 | 3 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 3 | 2 | 2 | 2 | 2 | 2 |
| | 7 | 8 | 7 | 0 | 8 | 1 | 9 | 8 | 6 | 7 | 9 | 0 | 7 | 9 | 9 | 8 | 6 | 0 | 7 | 0 | 6 | 6 | 7 | 7 | 7 |
| | 0 | 4 | 9 | 5 | 1 | 1 | 5 | 9 | 9 | 7 | 1 | 1 | 1 | 4 | 7 | 2 | 8 | 6 | 5 | 7 | 6 | 7 | 2 | 3 | 4 |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | X | | | X | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Sarcoma, metastatic, mesentery | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Schwannoma malignant, metastatic, skin | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Mediastinum, schwannoma malignant, metastatic, skin | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Schwannoma malignant, metastatic, skin | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Urinary bladder | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Leukemia granulocytic | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Lymphoma malignant | | | | | | | | | X | | | | | | | | | | X | X | | | | X | |

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Days on Study | 0 | 0 | 0 | 1 | 4 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 |
| | 0 | 3 | 4 | 7 | 1 | 0 | 5 | 6 | 8 | 2 | 3 | 3 | 4 | 4 | 5 | 7 | 8 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 1 |
| | 3 | 3 | 0 | 5 | 7 | 9 | 6 | 4 | 3 | 4 | 2 | 3 | 2 | 8 | 9 | 8 | 4 | 2 | 6 | 7 | 9 | 0 | 0 | 8 | 2 |
| Carcass ID Number | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 2 | 3 | 1 | 1 | 6 | 5 | 4 | 6 | 5 | 5 | 4 | 2 | 3 | 5 | 4 | 6 | 2 | 4 | 2 | 2 | 3 | 2 | 4 | 4 | 5 |
| | 9 | 7 | 6 | 8 | 0 | 4 | 2 | 5 | 2 | 5 | 8 | 0 | 4 | 7 | 7 | 4 | 7 | 5 | 2 | 4 | 6 | 6 | 3 | 1 | 9 |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | | + | + | | + | + | | | | + | | | | | | | |
| Pancreatic, hepatoblastoma, metastatic, liver | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Lymph node, mandibular | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Lymph node, mesenteric | M | A | + | + | + | + | + | + | + | A | + | + | A | + | M | + | + | + | A | + | + | + | + | + | + |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | A | + | + | + | + | + | + |
| Thymus | + | M | + | + | + | + | + | + | + | + | + | + | + | M | + | M | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Subcutaneous tissue, hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, sarcoma | | | | | | | X | | | | | | | X | | | | | | | | | X | | |
| Subcutaneous tissue, schwannoma malignant | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | + | | | | | | | | | | | | |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | X | | | | | | | | X | | |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | X | | | | | | | | | X | | |
| Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinum, sarcoma, metastatic, skin | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Nose | + | A | + | + | + | + | + | A | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + |
| Urinary bladder | + | A | + | + | M | + | + | A | + | + | + | + | + | A | + | + | + | + | A | A | + | + | + | + | + |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | | | | | | | X | | | | X | | X | X | | | | | | | | |

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Days on Study | 0 | 0 | 0 | 1 | 2 | 3 | 4 | 4 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 |
| | 1 | 1 | 1 | 8 | 9 | 6 | 3 | 7 | 1 | 2 | 7 | 9 | 1 | 2 | 7 | 8 | 8 | 9 | 9 | 0 | 0 | 2 | 2 | 2 |
| | 2 | 4 | 5 | 8 | 9 | 6 | 0 | 9 | 0 | 6 | 1 | 5 | 5 | 6 | 7 | 0 | 6 | 0 | 0 | 0 | 3 | 9 | 9 | 9 |
| Carcass ID Number | 4 | 4 | 3 | 4 | 3 | 3 | 4 | 3 | 3 | 3 | 4 | 3 | 3 | 3 | 4 | 4 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 3 |
| | 1 | 0 | 9 | 0 | 9 | 7 | 1 | 9 | 9 | 7 | 1 | 8 | 8 | 9 | 0 | 0 | 7 | 8 | 9 | 7 | 0 | 6 | 6 | 6 |
| | 3 | 5 | 5 | 6 | 1 | 1 | 4 | 9 | 4 | 7 | 5 | 8 | 4 | 8 | 2 | 4 | 2 | 6 | 3 | 4 | 9 | 6 | 7 | 8 |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | + | | | | | + | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | M | M | + |
| Lymph node, mesenteric | M | M | + | + | + | + | + | + | + | + | + | + | + | + | A | + | A | + | + | + | A | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | | | | | | | X | | | | | | | | |
| Spleen | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | M | + | + | + | + | M | M | + | M | M | A | M | M | + | I |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Subcutaneous tissue, sarcoma | | | | | | X | | | X | | | | | | | | | | | | | | | |
| Subcutaneous tissue, schwannoma malignant | | | | | | | | | | | | | | | | | | | | X | | | | |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | + | | | | | | | | | | |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | X | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | X | | | X | | | | | | X | | | |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | X | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | X | | X | | X | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | A | A | A | A | A | A | + | + | + |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | | | | | | X | | | | | | | | | | | | | | | |
| Mesothelioma malignant | | | | | | | | | | | | | | X | | X | | | | | | | | |

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

[illegible]

TABLE E3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|---|-------------|-------------|----------------|--------------|
| Liver: Hepatocellular Adenoma | | | | |
| Overall rate ^d | 37/49 (76%) | 39/50 (78%) | 43/50 (86%) | 34/50 (68%) |
| Adjusted rate ^b | 82.5% | 87.9% | 97.3% | 79.1% |
| Terminal rate ^c | 27/32 (84%) | 27/30 (90%) | 22/22 (100%) | 23/29 (79%) |
| First incidence (days) | 554 | 419 | 509 | 430 |
| Poly-3 test ^d | P=0.372N | P=0.336 | P=0.015 | P=0.442N |
| Liver: Hepatocellular Carcinoma | | | | |
| Overall rate | 13/49 (27%) | 23/50 (46%) | 33/50 (66%) | 41/50 (82%) |
| Adjusted rate | 29.8% | 55.0% | 78.1% | 97.1% |
| Terminal rate | 8/32 (25%) | 18/30 (60%) | 20/22 (91%) | 29/29 (100%) |
| First incidence (days) | 476 | 573 | 556 | 479 |
| Poly-3 test | P<0.001 | P=0.014 | P<0.001 | P<0.001 |
| Liver: Hepatocellular Adenoma or Carcinoma | | | | |
| Overall rate | 41/49 (84%) | 42/50 (84%) | 44/50 (88%) | 44/50 (88%) |
| Adjusted rate | 89.9% | 94.6% | 98.4% | 99.5% |
| Terminal rate | 29/32 (91%) | 29/30 (97%) | 22/22 (100%) | 29/29 (100%) |
| First incidence (days) | 476 | 419 | 509 | 430 |
| Poly-3 test | P=0.011 | P=0.323 | P=0.081 | P=0.045 |
| Liver: Hepatoblastoma | | | | |
| Overall rate | 1/49 (2%) | 2/50 (4%) | 9/50 (18%) | 16/50 (32%) |
| Adjusted rate | 2.4% | 4.9% | 21.6% | 39.6% |
| Terminal rate | 1/32 (3%) | 1/30 (3%) | 3/22 (14%) | 12/29 (41%) |
| First incidence (days) | 729 (T) | 599 | 564 | 510 |
| Poly-3 test | P<0.001 | P=0.493 | P=0.007 | P<0.001 |
| Liver: Hepatocellular Carcinoma or Hepatoblastoma | | | | |
| Overall rate | 13/49 (27%) | 23/50 (46%) | 36/50 (72%) | 43/50 (86%) |
| Adjusted rate | 29.8% | 55.0% | 82.8% | 99.0% |
| Terminal rate | 8/32 (25%) | 18/30 (60%) | 20/22 (91%) | 29/29 (100%) |
| First incidence (days) | 476 | 573 | 556 | 479 |
| Poly-3 test | P<0.001 | P=0.014 | P<0.001 | P<0.001 |
| Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma | | | | |
| Overall rate | 41/49 (84%) | 42/50 (84%) | 45/50 (90%) | 44/50 (88%) |
| Adjusted rate | 89.9% | 94.6% | 99.6% | 99.5% |
| Terminal rate | 29/32 (91%) | 29/30 (97%) | 22/22 (100%) | 29/29 (100%) |
| First incidence (days) | 476 | 419 | 509 | 430 |
| Poly-3 test | P=0.009 | P=0.323 | P=0.042 | P=0.045 |
| Lung: Alveolar/bronchiolar Adenoma | | | | |
| Overall rate | 2/50 (4%) | 3/50 (6%) | 0/50 (0%) | 3/50 (6%) |
| Adjusted rate | 4.7% | 7.2% | 0.0% | 7.8% |
| Terminal rate | 2/32 (6%) | 1/30 (3%) | 0/22 (0%) | 2/29 (7%) |
| First incidence (days) | 729 (T) | 555 | — ^e | 703 |
| Poly-3 test | P=0.463 | P=0.486 | P=0.254N | P=0.455 |
| Lung: Alveolar/bronchiolar Carcinoma | | | | |
| Overall rate | 2/50 (4%) | 1/50 (2%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 4.7% | 2.5% | 5.0% | 7.6% |
| Terminal rate | 1/32 (3%) | 1/30 (3%) | 1/22 (5%) | 0/29 (0%) |
| First incidence (days) | 662 | 729 (T) | 727 | 595 |
| Poly-3 test | P=0.287 | P=0.521N | P=0.665 | P=0.460 |

TABLE E3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|--|------------|----------------|------------|------------|
| Lung: Alveolar/bronchiolar Adenoma or Carcinoma | | | | |
| Overall rate | 4/50 (8%) | 4/50 (8%) | 2/50 (4%) | 5/50 (10%) |
| Adjusted rate | 9.3% | 9.6% | 5.0% | 12.7% |
| Terminal rate | 3/32 (9%) | 2/30 (7%) | 1/22 (5%) | 2/29 (7%) |
| First incidence (days) | 662 | 555 | 727 | 595 |
| Poly-3 test | P=0.399 | P=0.624 | P=0.374N | P=0.445 |
| Ovary: Cystadenoma | | | | |
| Overall rate | 4/47 (9%) | 3/49 (6%) | 1/46 (2%) | 0/49 (0%) |
| Adjusted rate | 9.9% | 7.6% | 2.7% | 0.0% |
| Terminal rate | 4/32 (13%) | 2/29 (7%) | 1/21 (5%) | 0/29 (0%) |
| First incidence (days) | 729 (T) | 696 | 729 (T) | — |
| Poly-3 test | P=0.029N | P=0.513N | P=0.210N | P=0.069N |
| Pituitary Gland (Pars Distalis): Adenoma | | | | |
| Overall rate | 8/47 (17%) | 9/44 (20%) | 6/42 (14%) | 2/46 (4%) |
| Adjusted rate | 19.7% | 25.0% | 17.1% | 5.7% |
| Terminal rate | 8/31 (26%) | 6/26 (23%) | 5/21 (24%) | 2/27 (7%) |
| First incidence (days) | 729 (T) | 608 | 700 | 729 (T) |
| Poly-3 test | P=0.041N | P=0.391 | P=0.502N | P=0.071N |
| Skin (Subcutaneous Tissue): Sarcoma | | | | |
| Overall rate | 2/50 (4%) | 2/50 (4%) | 3/50 (6%) | 4/50 (8%) |
| Adjusted rate | 4.7% | 4.9% | 7.4% | 9.9% |
| Terminal rate | 2/32 (6%) | 1/30 (3%) | 0/22 (0%) | 1/29 (3%) |
| First incidence (days) | 729 (T) | 573 | 556 | 299 |
| Poly-3 test | P=0.197 | P=0.679 | P=0.477 | P=0.311 |
| Thyroid Gland (Follicular Cell): Adenoma | | | | |
| Overall rate | 3/50 (6%) | 2/50 (4%) | 3/50 (6%) | 3/50 (6%) |
| Adjusted rate | 7.0% | 4.9% | 7.6% | 7.8% |
| Terminal rate | 3/32 (9%) | 1/30 (3%) | 3/22 (14%) | 3/29 (10%) |
| First incidence (days) | 729 (T) | 674 | 729 (T) | 729 (T) |
| Poly-3 test | P=0.472 | P=0.522N | P=0.628 | P=0.615 |
| All Organs: Hemangioma | | | | |
| Overall rate | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) | 3/50 (6%) |
| Adjusted rate | 0.0% | 0.0% | 2.5% | 7.7% |
| Terminal rate | 0/32 (0%) | 0/30 (0%) | 1/22 (5%) | 2/29 (7%) |
| First incidence (days) | — | — ^f | 729 (T) | 615 |
| Poly-3 test | P=0.017 | — ^f | P=0.485 | P=0.103 |
| All Organs: Hemangioma or Hemangiosarcoma | | | | |
| Overall rate | 0/50 (0%) | 0/50 (0%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 0.0% | 0.0% | 5.0% | 7.7% |
| Terminal rate | 0/32 (0%) | 0/30 (0%) | 1/22 (5%) | 2/29 (7%) |
| First incidence (days) | — | — | 723 | 615 |
| Poly-3 test | P=0.022 | — | P=0.221 | P=0.103 |
| All Organs: Malignant Lymphoma | | | | |
| Overall rate | 6/50 (12%) | 7/50 (14%) | 4/50 (8%) | 6/50 (12%) |
| Adjusted rate | 13.9% | 17.1% | 9.8% | 15.3% |
| Terminal rate | 2/32 (6%) | 5/30 (17%) | 0/22 (0%) | 5/29 (17%) |
| First incidence (days) | 687 | 599 | 624 | 510 |
| Poly-3 test | P=0.546N | P=0.460 | P=0.407N | P=0.554 |

TABLE E3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|--|-------------|--------------|--------------|--------------|
| All Organs: Benign Neoplasms | | | | |
| Overall rate | 40/50 (80%) | 41/50 (82%) | 43/50 (86%) | 36/50 (72%) |
| Adjusted rate | 85.5% | 91.5% | 97.3% | 83.7% |
| Terminal rate | 28/32 (88%) | 28/30 (93%) | 22/22 (100%) | 25/29 (86%) |
| First incidence (days) | 151 | 419 | 509 | 430 |
| Poly-3 test | P=0.445N | P=0.275 | P=0.035 | P=0.527N |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 26/50 (52%) | 30/50 (60%) | 40/50 (80%) | 44/50 (88%) |
| Adjusted rate | 56.0% | 69.7% | 90.1% | 99.2% |
| Terminal rate | 14/32 (44%) | 20/30 (67%) | 20/22 (91%) | 29/29 (100%) |
| First incidence (days) | 375 | 573 | 556 | 299 |
| Poly-3 test | P<0.001 | P=0.128 | P<0.001 | P<0.001 |
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 47/50 (94%) | 45/50 (90%) | 45/50 (90%) | 45/50 (90%) |
| Adjusted rate | 96.5% | 99.7% | 99.6% | 99.7% |
| Terminal rate | 31/32 (97%) | 30/30 (100%) | 22/22 (100%) | 29/29 (100%) |
| First incidence (days) | 151 | 419 | 509 | 299 |
| Poly-3 test | P=0.174 | P=0.348 | P=0.366 | P=0.347 |

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

^f Value of statistic cannot be computed.

TABLE E4
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F₁ Mice^a

| | Incidence in Controls | | | |
|-------------------------------------|---------------------------|-----------------------------|----------------|---|
| | Hepatocellular Adenoma | Hepatocellular Carcinoma | Hepatoblastoma | Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma |
| Overall Historical Incidence | | | | |
| Total | 150/289 (51.9%) | 55/289 (19.0%) | 0/289 | 173/289 (59.9%) |
| Standard deviation | 20.8% | 13.7% | | 21.3% |
| Range | 26%-80% | 8%-42% | | 32%-82% |

^a Data as of 1 August 1997

TABLE E5

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine^a

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|---------------------------------------|----------|----------|----------|----------|
| Disposition Summary | | | | |
| Animals initially in study | 50 | 50 | 50 | 50 |
| Early deaths | | | | |
| Accidental deaths | 3 | 6 | 4 | 5 |
| Moribund | 3 | 2 | 3 | 5 |
| Natural deaths | 12 | 12 | 21 | 11 |
| Survivors | | | | |
| Terminal sacrifice | 32 | 30 | 22 | 29 |
| Animals examined microscopically | 50 | 50 | 50 | 50 |
| Alimentary System | | | | |
| Gallbladder | (37) | (40) | (33) | (34) |
| Hyperplasia | | | | 1 (3%) |
| Intestine large, rectum | (44) | (48) | (47) | (47) |
| Artery, necrosis | | | | 1 (2%) |
| Intestine large, cecum | (44) | (49) | (40) | (45) |
| Edema | | | 1 (3%) | |
| Intestine small, jejunum | (42) | (47) | (38) | (43) |
| Peyer's patch, hyperplasia, lymphoid | 1 (2%) | | | |
| Intestine small, ileum | (43) | (48) | (37) | (41) |
| Peyer's patch, hyperplasia, lymphoid | | 1 (2%) | | |
| Liver | (49) | (50) | (50) | (50) |
| Basophilic focus | 1 (2%) | | | |
| Clear cell focus | 1 (2%) | 5 (10%) | 1 (2%) | 2 (4%) |
| Cyst | | | 1 (2%) | |
| Eosinophilic focus | 17 (35%) | 12 (24%) | 14 (28%) | 9 (18%) |
| Hematopoietic cell proliferation | 2 (4%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Hemorrhage | 1 (2%) | | | |
| Infiltration cellular, lymphocyte | 4 (8%) | | | |
| Mixed cell focus | 5 (10%) | 4 (8%) | 3 (6%) | |
| Necrosis | 5 (10%) | 2 (4%) | 5 (10%) | 7 (14%) |
| Vacuolization cytoplasmic, diffuse | 1 (2%) | | | 1 (2%) |
| Centrilobular, congestion | | | | 1 (2%) |
| Centrilobular, degeneration | | | 1 (2%) | 1 (2%) |
| Midzonal, vacuolization cytoplasmic | | | 1 (2%) | |
| Periportal, vacuolization cytoplasmic | | 2 (4%) | 1 (2%) | |
| Mesentery | (17) | (18) | (13) | (13) |
| Infiltration cellular, lymphocyte | 1 (6%) | | | |
| Inflammation, chronic active | 2 (12%) | | | |
| Fat, necrosis | 12 (71%) | 13 (72%) | 11 (85%) | 9 (69%) |
| Pancreas | (49) | (49) | (47) | (48) |
| Infiltration cellular, lymphocyte | 1 (2%) | 1 (2%) | | |
| Inflammation, chronic active | 1 (2%) | | | 2 (4%) |
| Acinus, atrophy | | 2 (4%) | 1 (2%) | 2 (4%) |
| Artery, inflammation, chronic | | | 1 (2%) | |
| Duct, cyst | | 1 (2%) | 2 (4%) | 2 (4%) |
| Salivary glands | (50) | (50) | (49) | (50) |
| Infiltration cellular, lymphocyte | 33 (66%) | 35 (70%) | 36 (73%) | 29 (58%) |
| Stomach, forestomach | (49) | (49) | (49) | (49) |
| Ulcer | 1 (2%) | | | |
| Epithelium, hyperplasia | 1 (2%) | | | |
| Stomach, glandular | (48) | (49) | (48) | (49) |
| Necrosis | 3 (6%) | 3 (6%) | 4 (8%) | 3 (6%) |
| Tooth | (2) | | | |
| Developmental malformation | 2 (100%) | | | |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE E5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|---|----------|----------|----------|----------|
| Cardiovascular System | | | | |
| Blood vessel | (48) | (47) | (47) | (47) |
| Aorta, inflammation, chronic active | 1 (2%) | | | |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy | 1 (2%) | | | |
| Inflammation, chronic active | 1 (2%) | | | |
| Mineralization | | | 1 (2%) | |
| Atrium, thrombosis | | | | 1 (2%) |
| Endocrine System | | | | |
| Adrenal cortex | (49) | (50) | (48) | (50) |
| Cytoplasmic alteration | 2 (4%) | | | 2 (4%) |
| Hematopoietic cell proliferation | | 1 (2%) | 1 (2%) | |
| Hemorrhage | 1 (2%) | | | 2 (4%) |
| Hyperplasia | 1 (2%) | | | |
| Capsule, hyperplasia | 41 (84%) | 35 (70%) | 39 (81%) | 37 (74%) |
| Adrenal medulla | (49) | (49) | (45) | (49) |
| Hyperplasia | 1 (2%) | 2 (4%) | | |
| Islets, pancreatic | (49) | (50) | (47) | (49) |
| Hyperplasia | | | 2 (4%) | 3 (6%) |
| Parathyroid gland | (31) | (29) | (30) | (36) |
| Infiltration cellular, lymphocyte | | | | 1 (3%) |
| Pituitary gland | (47) | (44) | (42) | (46) |
| Hemorrhage | | | | 1 (2%) |
| Pars distalis, angiectasis | | 1 (2%) | | 1 (2%) |
| Pars distalis, hyperplasia | 5 (11%) | 4 (9%) | 6 (14%) | 8 (17%) |
| Pars intermedia, hyperplasia | 1 (2%) | | | |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Infiltration cellular, lymphocyte | | 3 (6%) | | 3 (6%) |
| C-cell, hyperplasia | 1 (2%) | | | |
| Follicle, cyst | 4 (8%) | | 1 (2%) | |
| Follicular cell, hyperplasia | 14 (28%) | 21 (42%) | 22 (44%) | 23 (46%) |
| General Body System | | | | |
| Peritoneum | | | (2) | |
| Inflammation, chronic active | | | 1 (50%) | |
| Genital System | | | | |
| Clitoral gland | (47) | (48) | (48) | (45) |
| Atrophy | 45 (96%) | 43 (90%) | 45 (94%) | 43 (96%) |
| Cyst | 3 (6%) | | | |
| Inflammation, chronic | 2 (4%) | 2 (4%) | 1 (2%) | 4 (9%) |
| Inflammation, chronic active | 2 (4%) | | 3 (6%) | |
| Pigmentation | 2 (4%) | | 1 (2%) | 3 (7%) |
| Ovary | (47) | (49) | (46) | (49) |
| Angiectasis | | 1 (2%) | | |
| Cyst | 14 (30%) | 9 (18%) | 11 (24%) | 11 (22%) |
| Periovarian tissue, hyperplasia, lymphoid | | 1 (2%) | | |
| Uterus | (48) | (50) | (47) | (50) |
| Congestion | 1 (2%) | | | |
| Cyst | 3 (6%) | 3 (6%) | 5 (11%) | 2 (4%) |
| Hyperplasia, cystic | 44 (92%) | 43 (86%) | 38 (81%) | 39 (78%) |
| Inflammation, chronic active | 1 (2%) | | | 1 (2%) |
| Pigmentation | | | | 1 (2%) |

TABLE E5

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|---|----------|----------|----------|----------|
| Hematopoietic System | | | | |
| Bone marrow | (49) | (50) | (49) | (50) |
| Atrophy | 1 (2%) | 1 (2%) | | |
| Myeloid cell, hyperplasia | 1 (2%) | | | 2 (4%) |
| Lymph node | (10) | (10) | (7) | (7) |
| Iliac, hemorrhage | 1 (10%) | | | |
| Iliac, hyperplasia, lymphoid | 3 (30%) | | 2 (29%) | |
| Iliac, inflammation, chronic active | | | | 1 (14%) |
| Iliac, pigmentation | 1 (10%) | | | |
| Inguinal, hyperplasia, lymphoid | | | 1 (14%) | |
| Mediastinal, hemorrhage | 1 (10%) | | 1 (14%) | |
| Mediastinal, hyperplasia, plasma cell | | 1 (10%) | | |
| Mediastinal, inflammation, chronic active | 1 (10%) | | | |
| Mediastinal, pigmentation | | | 1 (14%) | |
| Renal, hemorrhage | | | 1 (14%) | |
| Renal, hyperplasia, lymphoid | 1 (10%) | | | |
| Lymph node, mandibular | (48) | (50) | (49) | (47) |
| Hemorrhage | 3 (6%) | | 1 (2%) | 1 (2%) |
| Hyperplasia, lymphoid | 2 (4%) | 2 (4%) | | |
| Lymph node, mesenteric | (48) | (47) | (43) | (45) |
| Angiectasis | | | 1 (2%) | 2 (4%) |
| Ectasia | | 1 (2%) | | |
| Hematopoietic cell proliferation | 1 (2%) | | | 1 (2%) |
| Hemorrhage | 4 (8%) | 2 (4%) | 3 (7%) | 2 (4%) |
| Hyperplasia, lymphoid | 1 (2%) | 1 (2%) | | |
| Artery, necrosis | | | | 1 (2%) |
| Spleen | (49) | (50) | (48) | (49) |
| Atrophy | | 1 (2%) | 1 (2%) | |
| Hematopoietic cell proliferation | 29 (59%) | 27 (54%) | 32 (67%) | 39 (80%) |
| Hemorrhage | | 1 (2%) | 1 (2%) | |
| Hyperplasia, lymphoid | 2 (4%) | 5 (10%) | 4 (8%) | 2 (4%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Pigmentation | 1 (2%) | | | 1 (2%) |
| Thymus | (45) | (44) | (46) | (39) |
| Atrophy | 11 (24%) | 11 (25%) | 13 (28%) | 10 (26%) |
| Ectopic parathyroid gland | 1 (2%) | | 2 (4%) | |
| Hyperplasia, lymphoid | 1 (2%) | | 1 (2%) | |
| Inflammation, acute | 1 (2%) | | | |
| Necrosis | 2 (4%) | 4 (9%) | 3 (7%) | 3 (8%) |
| Integumentary System | | | | |
| Mammary gland | (47) | (50) | (49) | (48) |
| Hyperplasia | 2 (4%) | 1 (2%) | | |
| Skin | (49) | (50) | (50) | (50) |
| Inflammation, chronic active | 1 (2%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Subcutaneous tissue, necrosis | | 1 (2%) | | |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Fibrous osteodystrophy | | 5 (10%) | 2 (4%) | |
| Hyperostosis | 1 (2%) | | | |

TABLE E5

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine

| | 0 ppm | 125 ppm | 250 ppm | 500 ppm |
|--|----------|----------|----------|----------|
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Cyst epithelial inclusion | | | | 1 (2%) |
| Hemorrhage | 1 (2%) | 1 (2%) | | |
| Infiltration cellular, histiocyte | | 1 (2%) | | |
| Mineralization | 25 (50%) | 27 (54%) | 18 (36%) | 19 (38%) |
| Meninges, inflammation, chronic active | 1 (2%) | | | |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Congestion | | 2 (4%) | 4 (8%) | 3 (6%) |
| Hemorrhage | 1 (2%) | | | 1 (2%) |
| Infiltration cellular, lymphocyte | 4 (8%) | 2 (4%) | | 1 (2%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Alveolar epithelium, hyperplasia | 5 (10%) | 3 (6%) | 1 (2%) | |
| Alveolus, infiltration cellular, histiocyte | 2 (4%) | | | 2 (4%) |
| Nose | (50) | (50) | (47) | (50) |
| Foreign body | 1 (2%) | | | |
| Olfactory epithelium, degeneration, hyaline | 19 (38%) | 27 (54%) | 35 (74%) | 36 (72%) |
| Olfactory epithelium, inflammation, chronic active | | | | 1 (2%) |
| Olfactory epithelium, necrosis | | 1 (2%) | | |
| Respiratory epithelium, degeneration, hyaline | 26 (52%) | 16 (32%) | 12 (26%) | 13 (26%) |
| Respiratory epithelium, hyperplasia | 12 (24%) | 8 (16%) | 12 (26%) | 4 (8%) |
| Respiratory epithelium, inflammation, chronic active | 3 (6%) | | | 1 (2%) |
| Respiratory epithelium, necrosis | | 1 (2%) | | |
| Special Senses System | | | | |
| None | | | | |
| Urinary System | | | | |
| Kidney | (49) | (50) | (49) | (49) |
| Infarct | 1 (2%) | 2 (4%) | 1 (2%) | |
| Infiltration cellular, plasma cell | | | | 1 (2%) |
| Infiltration cellular, lymphocyte | 4 (8%) | 2 (4%) | 5 (10%) | 2 (4%) |
| Nephropathy | 5 (10%) | 10 (20%) | 7 (14%) | 8 (16%) |
| Glomerulus, amyloid deposition | | | 1 (2%) | |
| Renal tubule, dilatation | | 1 (2%) | 2 (4%) | 2 (4%) |
| Renal tubule, pigmentation | | | 3 (6%) | 2 (4%) |
| Renal tubule, regeneration | | 1 (2%) | | 1 (2%) |
| Urinary bladder | (45) | (49) | (44) | (43) |
| Infiltration cellular, lymphocyte | 16 (36%) | 16 (33%) | 17 (39%) | 22 (51%) |

APPENDIX F

GENETIC TOXICOLOGY

| | |
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GENETIC TOXICOLOGY

***SALMONELLA TYPHIMURIUM* MUTAGENICITY TEST PROTOCOL**

Testing was performed as reported by Haworth *et al.* (1983). Pyridine was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37E C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37E C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of pyridine; 10,000 µg/plate was selected as the high dose. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose-related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1988). Pyridine was supplied as a coded aliquot by Radian Corporation. The high dose of pyridine did not exceed 5,000 µg/mL in the absence of toxicity. L5178Y mouse lymphoma cells were maintained at 37E C as suspension cultures in supplemented Fischer's medium; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring cells resistant to trifluorothymidine (TFT), subcultures were exposed to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day; to medium containing thymidine, hypoxanthine, and glycine for 1 day; and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with pyridine continued for 4 hours, at which time the medium plus pyridine was removed, and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, cells were plated in medium and soft agar supplemented with TFT for selection of TFT-resistant cells, and cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37E C in 5% CO₂ for 10 to 12 days. The test was initially performed without S9. Because a clearly positive response was not obtained, the test was repeated using freshly prepared S9 from the livers of Aroclor 1254-induced male 344 rats.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented by Caspary *et al.* (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for pyridine to be considered positive, i.e., capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Pyridine was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of pyridine; the high dose was limited by toxicity or, in the absence of toxicity, 5,000 µg/mL was selected as the high dose. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with pyridine in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing pyridine was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with pyridine, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no pyridine. Incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind, and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with pyridine for 11.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with pyridine and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. Two-hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose

resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

***DROSOPHILA MELANOGASTER* TEST PROTOCOLS**

The assays for induction sex-linked recessive lethal (SLRL) mutations and chromosomal reciprocal translocations (RTs) were performed with adult flies as described by Valencia *et al.* (1985) and Mason *et al.* (1992). Pyridine was supplied as a coded aliquot by Radian Corporation.

Sex-Linked Recessive Lethal Mutation Test: Pyridine was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no clearly positive response was obtained in the feeding experiments, it was retested by injection into adult males.

To administer pyridine by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament, and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2-0.3 μ L) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector that automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, was performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of pyridine at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Canton-S males were allowed to feed for 72 hours on a solution of pyridine in 5% sucrose. In the injection experiments, 24- to 72-hour old Canton-S males were treated with a solution of pyridine dissolved in saline and allowed to recover for 24 hours. A concurrent saline control group was also included. In the adult exposures, treated males were mated to three *Basc* females for 3 days and were given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier postmeiotic stages). F_1 heterozygous females were mated with their siblings and then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls (Mason *et al.*, 1992) using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered positive if the P value was less or equal to 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than or equal to 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or if the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A test was considered negative if the P value was greater than or equal to 0.10 or if the frequency in the treatment group was less than 0.10%.

Reciprocal Translocation Test: Because one of the injection experiments (Mason *et al.*, 1992) produced a positive result in the SLRL test, pyridine was assayed for induction of RTs using the same exposure method. The treatment regimen was essentially the same as that for the SLRL test, except that Canton-S males were mated *en masse* to marker (*bw;st* or *bw;e*) females. The females were transferred to fresh medium every 3 to 4 days for a period of about 3 weeks to produce a total of six broods. The results of the SLRL test were used to determine the germ cell stages most likely to be affected by pyridine. F_1 heterozygous males were backcrossed

individually to *bw;st* females, and the F₂ progeny were screened for pseudolinkage, which results from the induction of a translocation in a germ cell of the parental male. Flies suspected of carrying RTs were retested to confirm the findings. The translocation data were analyzed according to the conditional binomial response test of Kastenbaum and Bowman (1970).

MOUSE BONE MARROW CYTOGENETIC TEST PROTOCOLS

Chromosomal Aberrations Test: A dose range-finding study was performed in the absence of adequate toxicity information from the literature, and the highest dose was limited by toxicity. Pyridine was tested for induction of Abs in mouse bone marrow by two different protocols. The first protocol used a standard harvest time of 17 hours, and the second protocol used a delayed harvest time of 36 hours.

Male B6C3F₁ mice (10 animals per dose group) were injected intraperitoneally with pyridine dissolved in phosphate-buffered saline (PBS) (injection volume=0.4 mL). Solvent control mice received equivalent injections of PBS alone. The positive control was mitomycin C. The mice were subcutaneously implanted with a BrdU tablet (McFee *et al.*, 1983) 18 hours before the scheduled harvest. (For the standard protocol, this required BrdU implantation to precede injection with pyridine by 1 hour). The use of BrdU allowed selection of the appropriate cell population for scoring. (Abs induced by chemical administration are present in maximum number at the first metaphase following treatment; they decline in number during subsequent nuclear divisions due to cell death.) Two hours before sacrifice, the mice received an intraperitoneal injection of colchicine in saline. The animals were killed 17 or 36 hours after pyridine injection (18 hours after BrdU dosing). One or both femurs were removed, and the marrow was flushed out with PBS (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained and scored.

Fifty first-division metaphase cells were scored from each of eight animals per group. Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. The data were analyzed by a trend test (Margolin *et al.*, 1986).

Micronucleus Test: Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by pyridine exposure. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male B6C3F₁ mice were injected intraperitoneally three times at 24-hour intervals with pyridine dissolved in PBS; the total dosing volume was 0.4 mL. Solvent control animals were injected with 0.4 mL of PBS only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of five animals per dose group. In addition, the percentage of PCEs among the total erythrocyte population in the bone marrow was scored for each dose group as a measure of toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups using a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials

(as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitude of those effects.

RESULTS

Pyridine (100-10,000 µg/plate) was not mutagenic in *S. typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes (Haworth *et al.*, 1983; Table F1). Further, no significant increase in mutant frequencies was observed in L5178Y mouse lymphoma cells, tested with and without S9 metabolic activation (McGregor *et al.*, 1988; Table F2). In cytogenetic tests with cultured CHO cells, pyridine did not induce SCEs (Table F3) or Abs (Table F4), with or without S9. At the highest viable dose (1,673 µg/mL) tested for SCE induction in the absence of S9, pyridine induced marked cell cycle delay, and an extended culture time (31 hours) was used to allow sufficient cells to accumulate for analysis.

Pyridine was tested on three separate occasions in two different laboratories for induction of SLRL mutations in adult male *D. melanogaster* (Valencia *et al.*, 1985; Mason *et al.*, 1992; Foureman *et al.*, 1994; Table F5), and mixed results were obtained. In the first experiment (Valencia *et al.*, 1985), administration of pyridine by injection (7,000 ppm in aqueous 0.7% saline solution) gave negative ($P=0.225$) results, but feeding (600 and 700 ppm pyridine in aqueous 5% sucrose) produced an increase in recessive lethal mutations that was considered to be equivocal ($P=0.043$). A second experiment performed in the same laboratory using both injection (500 ppm) and feeding (729 ppm) yielded negative results (Foureman *et al.*, 1994). In the third experiment (Mason *et al.*, 1992) performed in a second laboratory, results of a feeding (500 ppm) experiment were negative ($P=0.998$), but administration of pyridine by injection (4,300 ppm) induced a significant increase in the frequency of SLRL mutations ($P=0.008$). Overall, pyridine was considered to be negative in SLRL tests when administered by feeding and equivocal when administered by injection. This positive result in the SLRL test led to the performance of a test for induction of RTs in germ cells of treated male *D. melanogaster* (Mason *et al.*, 1992; Table F6); results of this test were negative.

In vivo assays for chromosomal effects were conducted with male mice. No induction of Abs (Table F7) was noted in bone marrow cells at either of two sampling times (400-600 mg/kg pyridine; single injection), and no increase in the frequency of micronucleated PCEs (Table F8) was noted in bone marrow after intraperitoneal injection of pyridine (up to 500 mg/kg administered three times at 24-hour intervals).

In summary, with the exception of the single positive result obtained in a *D. melanogaster* SLRL assay, no indication of mutagenic activity was seen with pyridine in a variety of *in vitro* and *in vivo* assays for gene mutation and chromosomal damage.

TABLE F1
Mutagenicity of Pyridine in *Salmonella typhimurium*^a

| Strain | Dose (µg/plate) 1 | Revertants/plate ^b | | | | | |
|-------------------------------|-------------------------|-------------------------------|------------|-----------------|--------------|--------------|------------|
| | | ! S9 | | +10% hamster S9 | | +10% rat S9 | |
| | | Tr2al | Tr1al | Tr2al | Tr1al | Tr2al | Tr1al |
| TA100 | 0 | 115 ± 8.3 | 105 ± 3.5 | 116 ± 9.8 | 107 ± 14.4 | 113 ± 2.4 | 105 ± 8.0 |
| | 100 | 106 ± 6.4 | 113 ± 1.5 | 116 ± 5.4 | 131 ± 10.5 | 119 ± 6.4 | 107 ± 17.0 |
| | 333.3 | 93 ± 3.6 | 114 ± 5.5 | 103 ± 1.7 | 131 ± 8.6 | 129 ± 3.1 | 112 ± 15.1 |
| | 1,000 | 96 ± 5.2 | 114 ± 16.5 | 94 ± 2.3 | 115 ± 5.8 | 127 ± 1.3 | 117 ± 3.0 |
| | 3,333.3 | 93 ± 0.0 | 105 ± 4.6 | 121 ± 6.9 | 135 ± 12.2 | 122 ± 8.3 | 114 ± 3.9 |
| | 10,000 | 96 ± 10.7 | 117 ± 8.4 | 94 ± 2.8 | 148 ± 4.8 | 112 ± 8.1 | 119 ± 10.7 |
| Trial summary | | Negative | Negative | Negative | Equivocal | Negative | Negative |
| Positive control ^c | | 483 ± 7.2 | 416 ± 11.3 | 1,119 ± 119.8 | 2,115 ± 14.6 | 1,075 ± 30.0 | 549 ± 71.3 |
| TA1535 | 0 | 31 ± 0.7 | 21 ± 5.6 | 12 ± 2.3 | 12 ± 1.9 | 11 ± 1.8 | 14 ± 0.9 |
| | 100 | 34 ± 1.3 | 21 ± 4.8 | 9 ± 1.5 | 13 ± 2.3 | 14 ± 0.6 | 15 ± 3.7 |
| | 333.3 | 29 ± 5.6 | 18 ± 1.2 | 11 ± 2.1 | 11 ± 2.3 | 12 ± 1.3 | 12 ± 0.6 |
| | 1,000 | 27 ± 4.0 | 18 ± 1.5 | 10 ± 2.5 | 12 ± 1.8 | 14 ± 2.3 | 11 ± 1.2 |
| | 3,333.3 | 32 ± 3.8 | 17 ± 2.0 | 14 ± 1.9 | 11 ± 1.8 | 11 ± 1.7 | 12 ± 0.9 |
| | 10,000 | 33 ± 7.1 | 17 ± 4.0 | 14 ± 5.3 | 14 ± 1.2 | 13 ± 4.1 | 15 ± 1.9 |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 412 ± 9.4 | 346 ± 14.4 | 257 ± 13.8 | 266 ± 9.5 | 314 ± 14.9 | 167 ± 4.9 |
| TA1537 | 0 | 9 ± 1.3 | 5 ± 1.5 | 18 ± 3.5 | 10 ± 0.7 | 23 ± 2.1 | 6 ± 1.0 |
| | 100 | 13 ± 5.7 | 6 ± 1.2 | 20 ± 1.9 | 7 ± 0.6 | 20 ± 1.0 | 7 ± 0.7 |
| | 333.3 | 9 ± 0.6 | 6 ± 0.9 | 18 ± 4.9 | 8 ± 2.3 | 17 ± 2.2 | 4 ± 1.5 |
| | 1,000 | 14 ± 1.2 | 7 ± 1.0 | 18 ± 3.8 | 10 ± 2.2 | 22 ± 3.0 | 6 ± 1.0 |
| | 3,333.3 | 10 ± 3.0 | 5 ± 0.3 | 20 ± 4.7 | 9 ± 1.7 | 17 ± 2.7 | 5 ± 0.6 |
| | 10,000 | 14 ± 0.3 | 6 ± 0.9 | 17 ± 4.2 | 5 ± 1.8 | 18 ± 1.2 | 6 ± 1.5 |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 329 ± 159.1 | 847 ± 54.3 | 459 ± 52.4 | 411 ± 10.3 | 495 ± 52.6 | 239 ± 24.6 |
| TA98 | 0 | 35 ± 4.7 | 37 ± 3.5 | 49 ± 5.6 | 35 ± 2.3 | 31 ± 5.2 | 34 ± 3.2 |
| | 100 | 35 ± 4.9 | 33 ± 3.5 | 45 ± 2.0 | 39 ± 0.3 | 41 ± 2.4 | 40 ± 0.3 |
| | 333.3 | 35 ± 2.3 | 31 ± 5.9 | 39 ± 5.7 | 40 ± 0.9 | 36 ± 3.2 | 32 ± 5.1 |
| | 1,000 | 33 ± 4.9 | 29 ± 2.3 | 46 ± 7.5 | 37 ± 2.6 | 34 ± 1.5 | 38 ± 0.3 |
| | 3,333.3 | 25 ± 0.7 | 29 ± 3.4 | 50 ± 14.2 | 30 ± 4.7 | 33 ± 3.5 | 28 ± 1.8 |
| | 10,000 | 22 ± 3.5 | 27 ± 3.8 | 43 ± 6.4 | 43 ± 7.8 | 30 ± 5.6 | 26 ± 5.6 |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 691 ± 10.1 | 671 ± 57.5 | 570 ± 57.5 | 1,271 ± 7.8 | 574 ± 22.3 | 365 ± 22.9 |

^a Study was performed at SRI International. The detailed protocol and these data are presented by Haworth *et al.* (1983). 0 µg/plate was the solvent control.

^b Revertants are presented as mean ± standard error from three plates.

^c The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE F2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Pyridine^a

| Compound | Concentration (µg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction ^b | Average Mutant Fraction |
|--------------------------------------|--------------------------|------------------------------|---------------------------------|-----------------|---------------------------------|-------------------------------|
| Trial 1 | | | | | | |
| Medium^c | | | | | | |
| | | 112 | 102 | 95 | 28 | |
| | | 99 | 106 | 86 | 29 | |
| | | 108 | 103 | 100 | 31 | |
| | | 101 | 89 | 92 | 31 | 30 |
| Methyl methanesulfonate ^d | 15 | 43 | 26 | 239 | 186 | |
| | | 49 | 26 | 195 | 133 | 160* |
| Pyridine | 625 | 89 | 100 | 99 | 37 | |
| | | 105 | 102 | 95 | 30 | 34 |
| | 1,250 | 73 | 88 | 47 | 21 | |
| | | 86 | 101 | 80 | 31 | 26 |
| | 2,500 | 94 | 69 | 81 | 29 | |
| | | 78 | 71 | 56 | 24 | 26 |
| | 5,000 | 82 | 70 | 60 | 24 | |
| | | 88 | 77 | 113 | 43 | 34 |
| Trial 2 | | | | | | |
| Medium | | | | | | |
| | | 76 | 98 | 89 | 39 | |
| | | 99 | 102 | 136 | 46 | |
| | | 84 | 97 | 122 | 49 | |
| | | 65 | 102 | 120 | 62 | 49 |
| Methyl methanesulfonate | 15 | 27 | 23 | 440 | 550 | |
| | | 24 | 20 | 473 | 671 | 610* |
| Pyridine | 1,000 | 82 | 101 | 160 | 65 | |
| | | 58 | 90 | 106 | 61 | 63 |
| | 2,000 | 74 | 77 | 154 | 69 | |
| | | 68 | 78 | 167 | 81 | 75 |
| | 3,000 | 78 | 68 | 182 | 78 | |
| | | 71 | 76 | 161 | 76 | 77* |
| | 4,000 | 47 | 68 | 97 | 68 | |
| | | 55 | 76 | 154 | 94 | 81* |
| | 5,000 | 48 | 57 | 138 | 97 | |
| | | 69 | 66 | 151 | 73 | 85* |
| Trial 3 | | | | | | |
| Medium | | | | | | |
| | | 98 | 100 | 60 | 20 | |
| | | 108 | 110 | 67 | 21 | |
| | | 71 | 84 | 70 | 33 | |
| | | 102 | 106 | 85 | 28 | 25 |
| Methyl methanesulfonate | 15 | 25 | 14 | 126 | 166 | |
| | | 23 | 13 | 103 | 151 | 159* |
| Pyridine | 2,000 | 90 | 87 | 68 | 25 | |
| | | 79 | 85 | 53 | 22 | 24 |
| | 3,000 | 116 | 85 | 89 | 26 | |
| | | 90 | 79 | 64 | 24 | 25 |
| | 4,000 | 72 | 75 | 86 | 40 | |
| | | 88 | 79 | 145 | 55 | 47* |
| | 5,000 | 82 | 70 | 73 | 30 | |
| | | 89 | 67 | 79 | 30 | 30 |

TABLE F2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Pyridine

| Compound | Concentration (µg/mL) | Cloning Efficiency (%) | Relative Total Growth (%) | Mutant Count | Mutant Fraction | Average Mutant Fraction |
|---------------------------------|--------------------------|------------------------------|---------------------------------|-----------------|--------------------|-------------------------------|
| +S9 | | | | | | |
| Trial 1 | | | | | | |
| Medium | | 90 | 90 | 126 | 47 | 55 |
| | | 79 | 104 | 124 | 53 | |
| | | 83 | 102 | 137 | 55 | |
| | | 74 | 105 | 141 | 64 | |
| Methylcholanthrene ^d | 2.5 | 50 | 18 | 820 | 552 | 556* |
| | | 43 | 20 | 726 | 561 | |
| Pyridine | 1,000 | 82 | 88 | 133 | 54 | 56 |
| | | 89 | 96 | 152 | 57 | |
| | 2,000 | 94 | 77 | 230 | 82 | 68 |
| | | 77 | 99 | 123 | 53 | |
| | 3,000 | 77 | 86 | 204 | 89 | 71 |
| | | 89 | 80 | 140 | 52 | |
| | 4,000 | 100 | 70 | 167 | 55 | 59 |
| | | 78 | 79 | 147 | 63 | |
| 5,000 | 95 | 81 | 158 | 55 | 63 | |
| | 98 | 73 | 207 | 70 | | |
| Trial 2 | | | | | | |
| Solvent control | | 85 | 101 | 111 | 43 | 52 |
| | | 91 | 108 | 138 | 50 | |
| | | 100 | 93 | 188 | 62 | |
| | | 105 | 98 | 159 | 50 | |
| Methylcholanthrene | 2.5 | 54 | 24 | 686 | 421 | 436* |
| | | 58 | 28 | 791 | 451 | |
| Pyridine | 2,000 | 86 | 104 | 95 | 37 | 41 |
| | | 87 | 108 | 119 | 46 | |
| | 3,000 | 78 | 101 | 87 | 37 | 43 |
| | | 79 | 105 | 117 | 49 | |
| | 4,000 | 80 | 97 | 94 | 39 | 41 |
| | | 84 | 91 | 107 | 42 | |
| | 5,000 | 109 | 78 | 101 | 31 | 33 |
| | | 109 | 84 | 115 | 35 | |

* Positive response (P#0.05) versus the solvent control

^a Study was performed at Inveresk Research International. The detailed protocol and these data are presented by McGregor *et al.* (1988).

^b Mutant fraction=mutant cells/10⁶ clonable cells

^c Solvent control

^d Positive control

TABLE F3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Pyridine^a

| Compound | Concentration (µg/mL) | Total Cells Scored | No. of Chromosomes | No. of SCEs | SCEs/Chromosome | SCEs/Cell | Hrs in BrdU | Relative Change of SCEs/Chromosome ^b (%) |
|-------------------------------|-----------------------|--------------------|--------------------|-------------|-----------------|-----------|-------------------|---|
| ! S9 | | | | | | | | |
| Summary: Negative | | | | | | | | |
| Distilled water ^c | | 50 | 1,049 | 415 | 0.39 | 8.3 | 26.0 | |
| | | 50 | 1,049 | 424 | 0.40 | 8.5 | 31.0 ^e | |
| Mitomycin-C ^d | 0.001 | 50 | 1,049 | 665 | 0.63 | 13.3 | 26.0 | 56.84 |
| | 0.004 | 10 | 208 | 201 | 0.96 | 20.1 | 26.0 | 139.08 |
| Pyridine | 167 | 50 | 1,043 | 407 | 0.39 | 8.1 | 26.0 | ! 3.46 |
| | 502 | 50 | 1,049 | 437 | 0.41 | 8.7 | 26.0 | 3.07 |
| | 1,673 | 50 | 1,050 | 434 | 0.41 | 8.7 | 31.0 | 2.26 |
| | 5,020 | 0 | | | | | | |
| P=0.273 ^f | | | | | | | | |
| +S9 | | | | | | | | |
| Summary: Negative | | | | | | | | |
| Distilled water | | 50 | 1,050 | 389 | 0.37 | 7.8 | 26.0 | |
| Cyclophosphamide ^d | 0.125 | 50 | 1,051 | 598 | 0.56 | 12.0 | 26.0 | 53.58 |
| | 0.5 | 10 | 207 | 186 | 0.89 | 18.6 | 26.0 | 142.54 |
| Pyridine | 502 | 50 | 1,048 | 416 | 0.39 | 8.3 | 26.0 | 7.14 |
| | 1,673 | 50 | 1,051 | 421 | 0.40 | 8.4 | 26.0 | 8.12 |
| | 5,020 | 50 | 1,051 | 388 | 0.36 | 7.8 | 26.0 | ! 0.35 |
| P=0.494 | | | | | | | | |

^a Study was performed at SITEK Research Laboratories. The detailed protocol is presented by Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine

^b SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells

^c Solvent control

^d Positive control

^e Due to cell cycle delay, harvest time was extended to maximize the number of second-division metaphase cells available for analysis.

^f Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE F4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Pyridine^a

| Compound | Concentration (µg/mL) | Total Cells Scored | Number of Aberrations | Aberrations/Cell | Cells with Aberrations (%) |
|-------------------------------|-----------------------|--------------------|-----------------------|------------------|----------------------------|
| ! S9 | | | | | |
| Harvest time: 13.5 hours | | | | | |
| Summary: Negative | | | | | |
| Distilled water ^b | | 200 | 2 | 0.01 | 1.0 |
| Mitomycin-C ^c | 0.4 | 25 | 37 | 1.48 | 76.0 |
| Pyridine | 503 | 200 | 0 | 0.00 | 0.0 |
| | 1,081 | 200 | 0 | 0.00 | 0.0 |
| | 2,325 | 200 | 2 | 0.01 | 1.0 |
| P=0.450 ^d | | | | | |
| +S9 | | | | | |
| Harvest time: 13.5 hours | | | | | |
| Summary: Negative | | | | | |
| Distilled water | | 200 | 2 | 0.01 | 1.0 |
| Cyclophosphamide ^c | 20 | 25 | 42 | 1.68 | 48.0 |
| Pyridine | 1,081 | 200 | 1 | 0.01 | 0.5 |
| | 2,325 | 200 | 1 | 0.01 | 0.5 |
| | 5,000 | 200 | 3 | 0.02 | 1.5 |
| P=0.305 | | | | | |

^a Study was performed at SITEK Research Laboratories. The detailed protocol is presented by Galloway *et al.* (1987).

^b Solvent control

^c Positive control

^d Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE F5
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Pyridine^a

| Route of Exposure | Dose (ppm) | Incidence of Death (%) | Incidence of Sterility (%) | No. of Lethals/No. of X Chromosomes Tested | | | Total ^b |
|--|------------|------------------------|----------------------------|--|----------|----------|---|
| | | | | Mating 1 | Mating 2 | Mating 3 | |
| Study performed at Brown University ^c | | | | | | | |
| Feed | 600 | 5 | 0 | 0/1,116 | 1/1,123 | 1/1,136 | 2/3,375 (0.06%) |
| | 0 | | | 0/1,214 | 1/1,128 | 0/1,050 | 1/3,392 (0.03%) |
| | 700 | 20 | 2 | 4/1,027 | 1/1,069 | 0/1,082 | 5/3,178 (0.16%) |
| | 0 | | | 0/1,114 | 1/1,142 | 0/1,105 | 1/3,361 (0.03%) |
| Combined data set (600 ppm and 700 ppm trials): | | | | 4/2,143 | 2/2,192 | 1/2,218 | 7/6,553 (0.11%) |
| | | | | 0/2,328 | 2/2,270 | 0/2,155 | 2/6,753 (0.03%) P=0.043 ^d |
| Injection | 7,000 | 5 | 0 | 1/1,770 | 1/2,281 | 3/2,039 | 5/6,090 (0.08%) |
| | 0 | | | 1/2,170 | 2/2,750 | 0/1,379 | 3/6,299 (0.05%) P=0.225 |
| Feed | 729 | 22 | 0 | 1/1,724 | 0/2,664 | 1/1,121 | 2/5,509 (0.04%) |
| | 0 | | | 0/1,902 | 1/2,541 | 6/1,413 | 7/5,856 (0.12%) P=0.943 |
| Injection | 500 | 4 | 0 | 4/1,916 | 1/2,006 | 2/1,944 | 7/5,866 (0.12%) |
| | 0 | | | 2/1,908 | 1/1,933 | 0/1,921 | 3/5,762 (0.05%) P=0.108 |
| Study performed at University of Wisconsin, Madison ^e | | | | | | | |
| Feed | 500 | 12 | 1 | 1/2,063 | 0/1,989 | 0/1,666 | 1/5,718 (0.02%) |
| | 0 | | | 3/1,947 | 5/1,726 | 2/1,438 | 10/5,111 (0.20%) P=0.998 |
| Injection | 4,300 | 26 | 9 | 7/1,854 | 1/1,731 | 1/1,608 | 9/5,193 (0.17%) |
| | 0 | | | 3/4,163 | 2/3,949 | 1/3,285 | 6/11,397 (0.05%) P=0.008 |

^a The mean mutant frequency from 518 negative control experiments is 0.074% (Mason *et al.*, 1992).

^b Total number of lethal mutations/total number of X chromosomes tested for three mating trials

^c The detailed protocol and these data are presented by Valencia *et al.* (1985) (first two exposures) and Foureman (1994) (last 2 exposures).

^d Data from the 600 ppm and 700 ppm trials were combined to provide an adequate sample size for statistical analysis. The P value was generated from the combined data set.

^e The detailed protocol and these data are presented by Mason *et al.* (1992).

TABLE F6
Induction of Reciprocal Translocations in *Drosophila melanogaster* by Pyridine^a

| Route of Exposure | Dose (ppm) | Translocations/Total F ₁ Tested | | | | | | No. of Tests | Total No. of Translocations | Total Translocations (%) |
|--------------------|------------|--|----------|----------|----------|----------|-------|--------------|-----------------------------|--------------------------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | | | |
| Injection | 4,300 | 0/1,483 | 0/1,413 | 0/1,243 | 0/819 | 0/254 | 0/11 | 5,223 | 0 | 0 |
| Historical control | | 0/27,245 | 0/31,611 | 0/22,410 | 2/23,623 | 0/10,506 | 0/768 | 116,163 | 2 | 0.002 |

^a Study was performed at University of Wisconsin, Madison. The detailed protocol and these data are presented by Mason *et al.* (1992). Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).

TABLE F7
Induction of Chromosomal Aberrations in Mouse Bone Marrow Cells by Pyridine^a

| Compound | Dose (mg/kg) | Total Cells Scored | Total Aberrations (! gaps) | Cells with Aberrations ^b (%) |
|--|--------------|--------------------|----------------------------|---|
| Trial 1 | | | | |
| Sample time: 17 hours | | | | |
| Phosphate-buffered saline ^c | | 400 | 2 | 0.50 ± 0.33 |
| Mitomycin-C ^d | 1 | 400 | 11 | 2.25 ± 0.45 |
| | 2 | 400 | 48 | 9.50 ± 1.76 |
| Pyridine | 400 | 400 | 2 | 0.50 ± 0.50 |
| | 500 | 400 | 8 | 1.75 ± 0.59 |
| | 600 | 400 | 2 | 0.50 ± 0.33 |
| | | | | P=0.222 ^e |
| Trial 2 | | | | |
| Sample time: 36 hours | | | | |
| Phosphate-buffered saline | | 400 | 6 | 1.50 ± 0.63 |
| Mitomycin-C | 1 | 400 | 14 | 3.00 ± 0.85 |
| | 2 | 400 | 68 | 6.25 ± 2.31 |
| Pyridine | 400 | 400 | 3 | 0.75 ± 0.53 |
| | 500 | 400 | 6 | 1.50 ± 0.82 |
| | 600 | 400 | 0 | 0.00 ± 0.00 |
| | | | | P=0.948 |

^a Study was performed at Environmental Health Research and Testing, Inc. Fifty first-division metaphase cells were scored from each of eight mice per group. The detailed protocol and these data are presented by McFee (1989).

^b Mean ± standard error

^c Solvent control

^d Positive control

^e Significance tested by the one-tailed trend test; significant at P#0.05 (Margolin *et al.*, 1986)

TABLE F8
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Mice Treated with Pyridine by Intraperitoneal Injection^a

| Compound | Dose (mg/kg) | Number of Mice with Erythrocytes Scored | Micronucleated PCEs/ 1,000 PCEs ^b | PCEs ^b (%) |
|--|-----------------|---|---|--------------------------|
| Phosphate-buffered saline ^c | | 5 | 1.60 ± 0.51 | 52.52 ± 4.30 |
| Cyclophosphamide ^d | 15 | 5 | 11.50 ± 0.91 | 52.46 ± 1.71 |
| Pyridine | 31.25 | 5 | 1.40 ± 0.29 | 52.22 ± 1.11 |
| | 62.5 | 5 | 1.60 ± 0.43 | 53.04 ± 3.89 |
| | 125 | 5 | 1.10 ± 0.51 | 51.40 ± 3.66 |
| | 250 | 5 | 1.10 ± 0.37 | 51.22 ± 1.61 |
| | 500 | 5 | 1.20 ± 0.25 | 48.02 ± 1.88 |
| | | | P=0.811 ^e | |

^a Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol and these data are presented by Shelby *et al.* (1993).

^b Mean ± standard error

^c Solvent control

^d Positive control

^e Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P#0.025 (ILS, 1990)

APPENDIX G

HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

| | | |
|-----------------|--|------------|
| TABLE G1 | Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine | 276 |
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TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|--------------|---------------|--------------|---------------|------------------|----------------|
| Male | | | | | | |
| Hematology | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 9 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 10 | 10 | 10 | 10 | 9 |
| Week 13 | 10 | 10 | 10 | 10 | 10 | 10 |
| Automated hematocrit (%) | | | | | | |
| Day 5 | 46.8 ± 0.3 | 47.3 ± 0.5 | 48.1 ± 0.4* | 47.9 ± 0.5* | 47.9 ± 0.5 | 49.6 ± 0.4** |
| Day 20 | 49.6 ± 0.4 | 50.4 ± 0.3 | 48.2 ± 0.6 | 47.9 ± 0.3** | 47.8 ± 0.4** | 45.0 ± 0.4** |
| Week 13 | 46.9 ± 0.5 | 46.4 ± 0.3 | 46.8 ± 0.2 | 46.1 ± 0.3 | 45.9 ± 0.3 | 44.4 ± 0.7** |
| Manual hematocrit (%) | | | | | | |
| Day 5 | 44.2 ± 0.3 | 44.7 ± 0.6 | 45.2 ± 0.3* | 45.4 ± 0.5 | 45.5 ± 0.6 | 46.5 ± 0.5** |
| Day 20 | 48.0 ± 0.3 | 49.1 ± 0.6 | 46.6 ± 0.5 | 46.3 ± 0.5 | 46.5 ± 0.5* | 43.3 ± 0.5** |
| Week 13 | 45.7 ± 0.5 | 44.8 ± 0.4 | 45.6 ± 0.4 | 44.7 ± 0.2 | 44.3 ± 0.4* | 42.7 ± 0.7** |
| Hemoglobin (g/dL) | | | | | | |
| Day 5 | 15.3 ± 0.1 | 15.4 ± 0.1 | 15.6 ± 0.1 | 15.7 ± 0.1 | 15.8 ± 0.1** | 16.0 ± 0.2** |
| Day 20 | 16.3 ± 0.2 | 16.6 ± 0.1 | 15.7 ± 0.2 | 15.6 ± 0.1** | 15.7 ± 0.1* | 14.8 ± 0.2** |
| Week 13 | 15.4 ± 0.2 | 15.2 ± 0.1 | 15.3 ± 0.1 | 15.0 ± 0.2 | 14.9 ± 0.1* | 14.3 ± 0.2** |
| Erythrocytes (10 ⁶ /μL) | | | | | | |
| Day 5 | 8.40 ± 0.07 | 8.41 ± 0.13 | 8.54 ± 0.08 | 8.54 ± 0.07 | 8.58 ± 0.10 | 8.79 ± 0.08** |
| Day 20 | 8.92 ± 0.07 | 9.07 ± 0.07 | 8.62 ± 0.11 | 8.62 ± 0.07* | 8.66 ± 0.10 | 8.27 ± 0.13** |
| Week 13 | 9.09 ± 0.11 | 9.00 ± 0.07 | 9.12 ± 0.05 | 8.88 ± 0.07 | 8.87 ± 0.09 | 8.52 ± 0.20* |
| Reticulocytes (10 ⁶ /μL) | | | | | | |
| Day 5 | 0.18 ± 0.03 | 0.26 ± 0.05 | 0.20 ± 0.01 | 0.15 ± 0.02 | 0.15 ± 0.01 | 0.15 ± 0.01 |
| Day 20 | 0.18 ± 0.02 | 0.17 ± 0.02 | 0.18 ± 0.01 | 0.20 ± 0.01 | 0.19 ± 0.02 | 0.16 ± 0.01 |
| Week 13 | 0.17 ± 0.01 | 0.18 ± 0.02 | 0.19 ± 0.02 | 0.19 ± 0.02 | 0.19 ± 0.01 | 0.19 ± 0.02 |
| Nucleated erythrocytes (10 ³ /μL) | | | | | | |
| Day 5 | 0.01 ± 0.01 | 0.04 ± 0.02 | 0.00 ± 0.00 | 0.02 ± 0.02 | 0.04 ± 0.02 | 0.00 ± 0.00 |
| Day 20 | 0.00 ± 0.00 | 0.03 ± 0.02 | 0.01 ± 0.01 | 0.05 ± 0.02* | 0.02 ± 0.01 | 0.03 ± 0.02 |
| Week 13 | 0.02 ± 0.01 | 0.04 ± 0.02 | 0.03 ± 0.02 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.06 ± 0.02 |
| Mean cell volume (fL) | | | | | | |
| Day 5 | 55.8 ± 0.3 | 56.3 ± 0.4 | 56.4 ± 0.3 | 56.2 ± 0.3 | 55.9 ± 0.3 | 56.6 ± 0.2 |
| Day 20 | 55.5 ± 0.2 | 55.5 ± 0.4 | 55.8 ± 0.3 | 55.5 ± 0.3 | 55.3 ± 0.4 | 54.6 ± 0.5 |
| Week 13 | 51.6 ± 0.2 | 51.5 ± 0.2 | 51.4 ± 0.2 | 52.0 ± 0.3 | 51.8 ± 0.5 | 52.3 ± 0.7 |
| Mean cell hemoglobin (pg) | | | | | | |
| Day 5 | 18.3 ± 0.1 | 18.3 ± 0.1 | 18.3 ± 0.1 | 18.3 ± 0.1 | 18.5 ± 0.1 | 18.2 ± 0.1 |
| Day 20 | 18.3 ± 0.1 | 18.3 ± 0.1 | 18.3 ± 0.1 | 18.1 ± 0.1 | 18.1 ± 0.1 | 17.9 ± 0.1* |
| Week 13 | 17.0 ± 0.1 | 16.9 ± 0.1 | 16.8 ± 0.1 | 16.8 ± 0.1 | 16.8 ± 0.2 | 16.9 ± 0.2 |
| Mean cell hemoglobin concentration (g/dL) | | | | | | |
| Day 5 | 32.8 ± 0.2 | 32.4 ± 0.1 | 32.5 ± 0.1 | 32.7 ± 0.1 | 33.1 ± 0.2 | 32.3 ± 0.2 |
| Day 20 | 32.8 ± 0.2 | 33.0 ± 0.2 | 32.6 ± 0.2 | 32.7 ± 0.2 | 32.8 ± 0.2 | 32.9 ± 0.2 |
| Week 13 | 32.8 ± 0.1 | 32.9 ± 0.1 | 32.7 ± 0.1 | 32.4 ± 0.2 | 32.5 ± 0.1* | 32.3 ± 0.1** |
| Platelets (10 ³ /μL) | | | | | | |
| Day 5 | 908.7 ± 26.6 | 973.1 ± 33.9 | 957.3 ± 23.1 | 924.4 ± 27.9 | 880.7 ± 21.4 | 937.0 ± 19.9 |
| Day 20 | 856.9 ± 12.1 | 902.3 ± 31.3 | 880.4 ± 22.8 | 917.8 ± 15.1* | 1,065.7 ± 39.8** | 949.0 ± 28.2** |
| Week 13 | 731.0 ± 26.3 | 711.2 ± 12.1 | 732.3 ± 15.5 | 760.1 ± 15.5 | 791.8 ± 42.0* | 869.5 ± 65.4* |
| Leukocytes (10 ³ /μL) | | | | | | |
| Day 5 | 10.82 ± 0.44 | 11.72 ± 0.45 | 11.25 ± 0.43 | 10.36 ± 0.40 | 10.19 ± 0.45 | 10.82 ± 0.42 |
| Day 20 | 9.31 ± 0.42 | 11.48 ± 0.49* | 8.83 ± 0.22 | 9.32 ± 0.34 | 9.62 ± 0.51 | 9.42 ± 0.49 |
| Week 13 | 9.46 ± 0.43 | 10.24 ± 0.31 | 9.93 ± 0.50 | 9.96 ± 0.37 | 10.24 ± 0.49 | 11.26 ± 0.56 |
| Segmented neutrophils (10 ³ /μL) | | | | | | |
| Day 5 | 1.84 ± 0.14 | 1.66 ± 0.13 | 1.47 ± 0.16 | 1.60 ± 0.13 | 1.45 ± 0.13 | 1.77 ± 0.23 |
| Day 20 | 1.45 ± 0.15 | 1.68 ± 0.17 | 1.08 ± 0.13 | 1.28 ± 0.10 | 1.54 ± 0.22 | 1.00 ± 0.09 |
| Week 13 | 2.01 ± 0.20 | 1.84 ± 0.14 | 1.64 ± 0.21 | 1.78 ± 0.23 | 1.90 ± 0.16 | 2.16 ± 0.29 |

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|-----------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Male (continued) | | | | | | |
| Hematology (continued) | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 9 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 10 | 10 | 10 | 10 | 9 |
| Week 13 | 10 | 10 | 10 | 10 | 10 | 10 |
| Lymphocytes (10 ³ /μL) | | | | | | |
| Day 5 | 8.84 ± 0.39 | 9.95 ± 0.44 | 9.73 ± 0.46 | 8.61 ± 0.36 | 8.66 ± 0.39 | 9.02 ± 0.34 |
| Day 20 | 7.80 ± 0.32 | 9.73 ± 0.49* | 7.68 ± 0.27 | 8.00 ± 0.37 | 7.99 ± 0.48 | 8.32 ± 0.45 |
| Week 13 | 7.40 ± 0.37 | 8.37 ± 0.28 | 8.25 ± 0.48 | 8.15 ± 0.41 | 8.27 ± 0.51 | 9.03 ± 0.44* |
| Monocytes (10 ³ /μL) | | | | | | |
| Day 5 | 0.11 ± 0.04 | 0.05 ± 0.02 | 0.05 ± 0.02 | 0.09 ± 0.04 | 0.05 ± 0.02 | 0.01 ± 0.01 |
| Day 20 | 0.05 ± 0.02 | 0.03 ± 0.02 | 0.04 ± 0.02 | 0.01 ± 0.01 | 0.03 ± 0.01 | 0.06 ± 0.02 |
| Week 13 | 0.02 ± 0.01 | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.01 ± 0.01 | 0.03 ± 0.02 | 0.05 ± 0.04 |
| Basophils (10 ³ /μL) | | | | | | |
| Day 5 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 |
| Day 20 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 |
| Week 13 | 0.000 ± 0.000 | 0.011 ± 0.011 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 |
| Eosinophils (10 ³ /μL) | | | | | | |
| Day 5 | 0.02 ± 0.01 | 0.06 ± 0.03 | 0.01 ± 0.01 | 0.06 ± 0.03 | 0.03 ± 0.02 | 0.03 ± 0.02 |
| Day 20 | 0.01 ± 0.01 | 0.04 ± 0.02 | 0.04 ± 0.01 | 0.03 ± 0.02 | 0.06 ± 0.02 | 0.04 ± 0.02 |
| Week 13 | 0.02 ± 0.02 | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.02 ± 0.02 | 0.05 ± 0.02 | 0.02 ± 0.01 |
| Clinical Chemistry | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 10 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 10 | 10 | 10 | 10 | 9 |
| Week 13 | 10 | 10 | 10 | 10 | 10 | 10 |
| Urea nitrogen (mg/dL) | | | | | | |
| Day 5 | 23.1 ± 0.7 | 24.1 ± 0.8 | 25.5 ± 0.7 | 25.9 ± 0.9 | 24.1 ± 0.8 | 23.8 ± 0.8 |
| Day 20 | 24.3 ± 0.6 | 22.8 ± 0.6 | 23.9 ± 0.5 | 24.8 ± 0.4 | 23.2 ± 0.5 | 25.0 ± 0.5 |
| Week 13 | 25.1 ± 0.4 | 23.1 ± 0.7 | 23.9 ± 0.6 | 23.9 ± 0.7 | 25.0 ± 1.0 | 25.3 ± 1.1 |
| Creatinine (mg/dL) | | | | | | |
| Day 5 | 0.49 ± 0.01 | 0.51 ± 0.02 | 0.53 ± 0.02 | 0.49 ± 0.01 | 0.51 ± 0.01 | 0.50 ± 0.01 |
| Day 20 | 0.61 ± 0.03 | 0.56 ± 0.03 | 0.59 ± 0.02 | 0.60 ± 0.02 | 0.60 ± 0.03 | 0.61 ± 0.02 |
| Week 13 | 0.59 ± 0.02 | 0.55 ± 0.03 | 0.60 ± 0.03 | 0.60 ± 0.04 | 0.59 ± 0.03 | 0.64 ± 0.03 |
| Total protein (g/dL) | | | | | | |
| Day 5 | 6.3 ± 0.1 | 6.4 ± 0.1 | 6.6 ± 0.1 | 6.5 ± 0.1 | 6.4 ± 0.1 | 6.3 ± 0.1 |
| Day 20 | 6.8 ± 0.1 | 7.0 ± 0.1 | 7.1 ± 0.1 | 7.1 ± 0.1 | 7.1 ± 0.1 | 7.1 ± 0.1 |
| Week 13 | 6.4 ± 0.1 | 6.5 ± 0.1 | 6.8 ± 0.1* | 6.9 ± 0.1** | 7.1 ± 0.1** | 6.8 ± 0.1** |
| Albumin (g/dL) | | | | | | |
| Day 5 | 3.5 ± 0.1 | 3.6 ± 0.1 | 3.8 ± 0.1* | 3.7 ± 0.1* | 3.6 ± 0.1 | 3.6 ± 0.1 |
| Day 20 | 3.8 ± 0.1 | 4.0 ± 0.1 | 4.0 ± 0.1 | 4.0 ± 0.1 | 4.1 ± 0.1** | 3.9 ± 0.1 |
| Week 13 | 3.5 ± 0.1 | 3.6 ± 0.1 | 3.9 ± 0.1** | 3.8 ± 0.0** | 4.0 ± 0.0** | 3.9 ± 0.1** |
| Alanine aminotransferase (IU/L) | | | | | | |
| Day 5 | 42 ± 2 | 46 ± 1 | 51 ± 1** | 47 ± 1 | 60 ± 11 | 46 ± 1 |
| Day 20 | 53 ± 3 | 44 ± 3 | 40 ± 1* | 39 ± 2** | 49 ± 6 | 54 ± 6 |
| Week 13 | 60 ± 2 | 56 ± 4 | 52 ± 5 | 44 ± 2* | 50 ± 3 | 583 ± 268 |
| Alkaline phosphatase (IU/L) | | | | | | |
| Day 5 | 441 ± 15 | 468 ± 8 | 454 ± 16 | 423 ± 9 | 465 ± 10 | 456 ± 10 |
| Day 20 | 411 ± 11 | 302 ± 12** | 385 ± 14** | 320 ± 14** | 275 ± 21** | 331 ± 10** |
| Week 13 | 236 ± 6 | 219 ± 4 | 223 ± 6 | 203 ± 3* | 176 ± 8** | 278 ± 25 |

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|-----------------------|-----------------------|--------------|---------------|-----------------------|-----------------------|
| Male (continued) | | | | | | |
| Clinical Chemistry (continued) | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 10 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 10 | 10 | 10 | 10 | 9 |
| Week 13 | 10 | 10 | 10 | 10 | 10 | 10 |
| Creatine kinase (U/L) | | | | | | |
| Day 5 | 275 ± 63 | 260 ± 66 | 262 ± 43 | 183 ± 17 | 244 ± 33 ^b | 193 ± 21 |
| Day 20 | 169 ± 14 ^b | 241 ± 31 ^b | 167 ± 14 | 198 ± 20 | 180 ± 20 | 171 ± 28 |
| Week 13 | 234 ± 62 | 243 ± 63 | 223 ± 58 | 202 ± 56 | 339 ± 115 | 161 ± 32 ^b |
| Sorbitol dehydrogenase (IU/L) | | | | | | |
| Day 5 | 8 ± 0 | 9 ± 0 | 10 ± 1* | 9 ± 1 | 27 ± 17 | 11 ± 0** |
| Day 20 | 10 ± 0 | 8 ± 0 | 10 ± 1 | 10 ± 1 | 39 ± 13 | 23 ± 7 |
| Week 13 | 12 ± 1 | 11 ± 1 | 10 ± 1 | 10 ± 1 | 12 ± 1 | 395 ± 217 |
| Bile acids (μmol/L) | | | | | | |
| Day 5 | 33.5 ± 4.0 | 34.7 ± 3.5 | 38.6 ± 7.5 | 26.6 ± 1.7 | 45.9 ± 7.3 | 40.6 ± 5.1 |
| Day 20 | 28.3 ± 3.2 | 40.3 ± 3.7* | 26.6 ± 3.7 | 30.3 ± 2.7 | 61.0 ± 6.1** | 59.6 ± 7.6** |
| Week 13 | 30.5 ± 4.7 | 29.5 ± 4.2 | 26.0 ± 3.9 | 40.3 ± 7.7 | 62.1 ± 12.9* | 150.0 ± 19.7** |
| Female | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 10 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| Week 13 | 10 | 10 | 10 | 10 | 10 | 8 |
| Hematology | | | | | | |
| Automated hematocrit (%) | | | | | | |
| Day 5 | 48.4 ± 0.5 | 48.9 ± 0.5 | 50.3 ± 0.6 | 48.6 ± 0.6 | 50.7 ± 0.7 | 50.5 ± 1.0 |
| Day 20 | 48.2 ± 0.4 | 47.4 ± 0.5 | 47.8 ± 0.3 | 47.0 ± 0.5 | 45.5 ± 0.6** | 48.2 ± 1.0 |
| Week 13 | 46.5 ± 0.3 | 45.4 ± 0.3* | 45.5 ± 0.3* | 43.5 ± 0.5** | 43.1 ± 0.3** | 43.8 ± 0.4** |
| Manual hematocrit (%) | | | | | | |
| Day 5 | 44.9 ± 0.7 | 45.5 ± 0.4 | 46.9 ± 0.4 | 45.5 ± 0.6 | 46.9 ± 0.5 | 47.0 ± 0.9 |
| Day 20 | 46.7 ± 0.3 | 45.8 ± 0.6 | 46.3 ± 0.2 | 45.5 ± 0.4 | 44.4 ± 0.6* | 47.4 ± 0.9 |
| Week 13 | 44.8 ± 0.3 | 44.0 ± 0.3 | 44.0 ± 0.4 | 41.3 ± 0.8** | 40.9 ± 0.4** | 41.5 ± 0.5** |
| Hemoglobin (g/dL) | | | | | | |
| Day 5 | 16.0 ± 0.1 | 16.0 ± 0.2 | 16.4 ± 0.1 | 15.9 ± 0.2 | 16.6 ± 0.2 | 16.5 ± 0.3 |
| Day 20 | 16.6 ± 0.2 | 16.3 ± 0.1 | 16.3 ± 0.1 | 15.8 ± 0.1** | 15.6 ± 0.2** | 16.2 ± 0.3** |
| Week 13 | 15.8 ± 0.1 | 15.3 ± 0.1** | 15.2 ± 0.1** | 14.4 ± 0.2** | 14.2 ± 0.1** | 14.3 ± 0.1** |
| Erythrocytes (10 ⁶ /μL) | | | | | | |
| Day 5 | 7.96 ± 0.07 | 7.97 ± 0.11 | 8.19 ± 0.11 | 7.86 ± 0.09 | 8.30 ± 0.11 | 8.18 ± 0.21 |
| Day 20 | 8.25 ± 0.09 | 8.06 ± 0.08 | 8.14 ± 0.07 | 7.92 ± 0.10 | 7.85 ± 0.09 | 8.43 ± 0.18 |
| Week 13 | 8.66 ± 0.06 | 8.43 ± 0.04** | 8.40 ± 0.11* | 7.94 ± 0.11** | 7.93 ± 0.10** | 8.17 ± 0.11** |
| Reticulocytes (10 ⁶ /μL) | | | | | | |
| Day 5 | 0.18 ± 0.02 | 0.17 ± 0.01 | 0.18 ± 0.02 | 0.13 ± 0.01 | 0.19 ± 0.02 | 0.16 ± 0.01 |
| Day 20 | 0.16 ± 0.01 | 0.16 ± 0.02 | 0.16 ± 0.01 | 0.18 ± 0.01 | 0.17 ± 0.02 | 0.17 ± 0.01 |
| Week 13 | 0.15 ± 0.01 | 0.15 ± 0.01 | 0.15 ± 0.01 | 0.15 ± 0.01 | 0.15 ± 0.01 | 0.17 ± 0.01 |
| Nucleated erythrocytes (10 ³ /μL) | | | | | | |
| Day 5 | 0.03 ± 0.03 | 0.05 ± 0.02 | 0.04 ± 0.03 | 0.06 ± 0.02 | 0.04 ± 0.02 | 0.04 ± 0.03 |
| Day 20 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.02 ± 0.01 | 0.01 ± 0.01 | 0.01 ± 0.01 |
| Week 13 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.03 ± 0.01 | 0.03 ± 0.02 | 0.01 ± 0.01 | 0.00 ± 0.00 |

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|---|---------------|---------------|---------------|---------------------------|---------------|-------------------------|
| Female (continued) | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 10 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| Week 13 | 10 | 10 | 10 | 10 | 10 | 8 |
| Hematology (continued) | | | | | | |
| Mean cell volume (fL) | | | | | | |
| Day 5 | 60.9 ± 0.4 | 61.6 ± 0.5 | 61.6 ± 0.3 | 61.7 ± 0.4 | 61.3 ± 0.3 | 61.7 ± 0.7 |
| Day 20 | 58.4 ± 0.4 | 58.7 ± 0.3 | 58.7 ± 0.3 | 59.4 ± 0.5 | 58.0 ± 0.3 | 57.3 ± 0.4 |
| Week 13 | 53.7 ± 0.2 | 54.0 ± 0.1 | 54.2 ± 0.6 | 54.2 ± 0.2 | 54.4 ± 0.4 | 53.6 ± 0.3 |
| Mean cell hemoglobin (pg) | | | | | | |
| Day 5 | 20.1 ± 0.2 | 20.1 ± 0.2 | 20.1 ± 0.2 | 20.2 ± 0.2 | 20.0 ± 0.1 | 20.2 ± 0.2 ^b |
| Day 20 | 20.1 ± 0.1 | 20.2 ± 0.1 | 20.0 ± 0.1 | 19.9 ± 0.1 | 19.8 ± 0.1 | 19.3 ± 0.1** |
| Week 13 | 18.2 ± 0.1 | 18.1 ± 0.1 | 18.2 ± 0.2 | 18.2 ± 0.2 | 18.0 ± 0.2** | 17.5 ± 0.2** |
| Mean cell hemoglobin concentration (g/dL) | | | | | | |
| Day 5 | 33.1 ± 0.2 | 32.7 ± 0.1 | 32.7 ± 0.3 | 32.7 ± 0.3 | 32.7 ± 0.2 | 32.7 ± 0.2 |
| Day 20 | 34.4 ± 0.2 | 34.4 ± 0.2 | 34.0 ± 0.2 | 33.7 ± 0.2 | 34.2 ± 0.3 | 33.7 ± 0.2* |
| Week 13 | 34.0 ± 0.1 | 33.7 ± 0.2 | 33.5 ± 0.1* | 33.1 ± 0.2** | 33.0 ± 0.1** | 32.7 ± 0.2** |
| Platelets (10 ³ /μL) | | | | | | |
| Day 5 | 941.7 ± 30.3 | 885.4 ± 26.5 | 971.4 ± 26.3 | 906.8 ± 11.8 ^b | 863.3 ± 21.2 | 857.5 ± 61.5 |
| Day 20 | 930.8 ± 22.3 | 885.0 ± 28.0 | 884.6 ± 44.3 | 982.5 ± 23.9 | 919.7 ± 16.9 | 812.6 ± 61.7 |
| Week 13 | 721.5 ± 17.2 | 741.0 ± 9.5 | 729.4 ± 32.6 | 738.5 ± 38.4 | 759.2 ± 36.4 | 751.3 ± 45.7 |
| Leukocytes (10 ³ /μL) | | | | | | |
| Day 5 | 10.19 ± 0.41 | 9.35 ± 0.34 | 8.84 ± 0.35 | 8.67 ± 0.26 | 8.97 ± 0.50 | 8.36 ± 0.56* |
| Day 20 | 9.54 ± 0.29 | 9.60 ± 0.34 | 9.15 ± 0.42 | 9.41 ± 0.32 | 9.05 ± 0.35 | 8.95 ± 0.43 |
| Week 13 | 8.01 ± 0.32 | 8.38 ± 0.18 | 8.35 ± 0.23 | 7.93 ± 0.47 | 8.89 ± 0.28 | 8.70 ± 0.49 |
| Segmented neutrophils (10 ³ /μL) | | | | | | |
| Day 5 | 1.18 ± 0.18 | 1.48 ± 0.22 | 1.17 ± 0.13 | 0.98 ± 0.12 | 1.20 ± 0.23 | 1.15 ± 0.17 |
| Day 20 | 1.31 ± 0.14 | 1.49 ± 0.19 | 1.32 ± 0.13 | 1.44 ± 0.17 | 1.41 ± 0.17 | 1.87 ± 0.25 |
| Week 13 | 1.55 ± 0.15 | 1.48 ± 0.18 | 1.42 ± 0.09 | 1.39 ± 0.14 | 1.62 ± 0.19 | 1.27 ± 0.16 |
| Lymphocytes (10 ³ /μL) | | | | | | |
| Day 5 | 8.89 ± 0.42 | 7.81 ± 0.43 | 7.61 ± 0.41 | 7.64 ± 0.28 | 7.93 ± 0.52 | 7.14 ± 0.62 |
| Day 20 | 8.18 ± 0.32 | 8.06 ± 0.42 | 7.75 ± 0.46 | 7.82 ± 0.26 | 7.54 ± 0.36 | 6.99 ± 0.48 |
| Week 13 | 6.41 ± 0.23 | 6.87 ± 0.23 | 6.86 ± 0.24 | 6.42 ± 0.41 | 7.20 ± 0.28 | 7.40 ± 0.48 |
| Monocytes (10 ³ /μL) | | | | | | |
| Day 5 | 0.11 ± 0.04 | 0.03 ± 0.02 | 0.04 ± 0.02 | 0.04 ± 0.02 | 0.04 ± 0.01 | 0.03 ± 0.01 |
| Day 20 | 0.05 ± 0.02 | 0.04 ± 0.03 | 0.04 ± 0.02 | 0.11 ± 0.03 | 0.08 ± 0.04 | 0.07 ± 0.04 |
| Week 13 | 0.04 ± 0.01 | 0.02 ± 0.01 | 0.03 ± 0.01 | 0.04 ± 0.02 | 0.04 ± 0.02 | 0.01 ± 0.01 |
| Basophils (10 ³ /μL) | | | | | | |
| Day 5 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 |
| Day 20 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 |
| Week 13 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 |
| Eosinophils (10 ³ /μL) | | | | | | |
| Day 5 | 0.01 ± 0.01 | 0.03 ± 0.02 | 0.03 ± 0.01 | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.05 ± 0.03 |
| Day 20 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.04 ± 0.03 | 0.04 ± 0.02 | 0.02 ± 0.01 | 0.03 ± 0.02 |
| Week 13 | 0.02 ± 0.01 | 0.03 ± 0.01 | 0.04 ± 0.02 | 0.05 ± 0.02 | 0.04 ± 0.01 | 0.03 ± 0.02 |

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|---------------------------------|-------------|-------------|-------------|-----------------------|-------------|--------------------------|
| Female (continued) | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 10 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| Week 13 | 10 | 10 | 10 | 10 | 10 | 8 |
| Clinical Chemistry | | | | | | |
| Urea nitrogen (mg/dL) | | | | | | |
| Day 5 | 20.9 ± 1.0 | 21.2 ± 2.0 | 20.6 ± 0.8 | 20.3 ± 1.0 | 24.0 ± 1.0 | 22.9 ± 0.7 |
| Day 20 | 21.5 ± 0.7 | 22.0 ± 1.3 | 22.1 ± 1.1 | 22.6 ± 0.6 | 22.0 ± 0.6 | 25.9 ± 1.4 |
| Week 13 | 21.0 ± 0.8 | 20.4 ± 0.8 | 21.5 ± 1.2 | 18.3 ± 0.6 | 19.8 ± 0.7 | 23.4 ± 1.3 |
| Creatinine (mg/dL) | | | | | | |
| Day 5 | 0.55 ± 0.02 | 0.55 ± 0.03 | 0.51 ± 0.01 | 0.52 ± 0.03 | 0.58 ± 0.01 | 0.56 ± 0.02 |
| Day 20 | 0.58 ± 0.02 | 0.56 ± 0.03 | 0.61 ± 0.02 | 0.56 ± 0.03 | 0.57 ± 0.02 | 0.59 ± 0.02 ^b |
| Week 13 | 0.62 ± 0.02 | 0.60 ± 0.01 | 0.63 ± 0.03 | 0.61 ± 0.02 | 0.60 ± 0.03 | 0.61 ± 0.05 |
| Total protein (g/dL) | | | | | | |
| Day 5 | 6.0 ± 0.1 | 6.2 ± 0.1 | 6.7 ± 0.0** | 6.2 ± 0.1 | 6.5 ± 0.1** | 6.0 ± 0.1 |
| Day 20 | 6.4 ± 0.1 | 6.6 ± 0.1 | 6.5 ± 0.1 | 6.8 ± 0.1* | 6.9 ± 0.1** | 6.8 ± 0.1** |
| Week 13 | 6.8 ± 0.1 | 6.6 ± 0.1 | 6.7 ± 0.1 | 6.8 ± 0.1 | 7.0 ± 0.1 | 6.7 ± 0.1 |
| Albumin (g/dL) | | | | | | |
| Day 5 | 3.7 ± 0.0 | 3.7 ± 0.1 | 4.0 ± 0.1** | 3.7 ± 0.1 | 3.9 ± 0.1* | 3.8 ± 0.1 |
| Day 20 | 3.5 ± 0.1 | 3.6 ± 0.1 | 3.7 ± 0.1 | 3.8 ± 0.1** | 4.1 ± 0.1** | 4.0 ± 0.1** |
| Week 13 | 3.9 ± 0.1 | 3.9 ± 0.0 | 4.0 ± 0.1 | 4.0 ± 0.1 | 4.0 ± 0.1 | 4.0 ± 0.1 |
| Alanine aminotransferase (IU/L) | | | | | | |
| Day 5 | 36 ± 1 | 34 ± 1 | 33 ± 1 | 35 ± 2 | 45 ± 5 | 432 ± 294 |
| Day 20 | 35 ± 1 | 33 ± 2 | 30 ± 1 | 28 ± 1* | 29 ± 2* | 1,295 ± 1,133 |
| Week 13 | 40 ± 1 | 31 ± 2** | 33 ± 2* | 30 ± 1** | 30 ± 1** | 141 ± 72 |
| Alkaline phosphatase (IU/L) | | | | | | |
| Day 5 | 419 ± 7 | 375 ± 11* | 367 ± 7** | 368 ± 8** | 405 ± 10 | 410 ± 12 |
| Day 20 | 357 ± 8 | 328 ± 5** | 315 ± 7** | 287 ± 3** | 283 ± 6** | 314 ± 18** |
| Week 13 | 210 ± 5 | 193 ± 5 | 176 ± 4** | 162 ± 7** | 168 ± 5** | 209 ± 17** |
| Creatine kinase (IU/L) | | | | | | |
| Day 5 | 195 ± 28 | 230 ± 43 | 257 ± 22 | 207 ± 21 ^b | 300 ± 27** | 288 ± 39* |
| Day 20 | 266 ± 74 | 222 ± 53 | 208 ± 45 | 175 ± 38 | 143 ± 9 | 144 ± 15 ^b |
| Week 13 | 169 ± 23 | 119 ± 19 | 187 ± 42 | 210 ± 40 | 159 ± 20 | 240 ± 70 |
| Sorbitol dehydrogenase (IU/L) | | | | | | |
| Day 5 | 8 ± 1 | 7 ± 0 | 6 ± 1 | 7 ± 0 | 39 ± 20 | 111 ± 91 |
| Day 20 | 8 ± 1 | 9 ± 1 | 10 ± 0 | 10 ± 0 | 17 ± 6** | 383 ± 162** ^b |
| Week 13 | 8 ± 0 | 9 ± 0 | 8 ± 1 | 9 ± 1 | 10 ± 1 | 289 ± 204** |
| Bile acids (μmol/L) | | | | | | |
| Day 5 | 32.3 ± 3.4 | 28.3 ± 5.1 | 20.9 ± 2.8 | 43.0 ± 5.9 | 39.3 ± 11.2 | 69.2 ± 25.7 |
| Day 20 | 34.1 ± 3.9 | 37.0 ± 5.9 | 41.1 ± 6.1 | 40.0 ± 8.9 | 55.0 ± 4.9* | 202.0 ± 114.1** |
| Week 13 | 47.3 ± 9.8 | 39.5 ± 4.9 | 38.0 ± 5.6 | 38.9 ± 4.6 | 54.5 ± 7.9 | 87.3 ± 21.8 |

* Significantly different (P#0.05) from the control group by Dunn's or Shirley's test

** P#0.01

^a Mean ± standard error. Statistical tests were performed on unrounded data.

^b n=9

TABLE G2
Hematology and Clinical Chemistry Data for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine^a

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--|----------------|----------------|----------------|----------------|----------------|----------------|
| Hematology | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 10 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 9 | 9 | 9 | 10 | 10 |
| Week 13 | 10 | 10 | 10 | 10 | 9 | 10 |
| Automated hematocrit (%) | | | | | | |
| Day 5 | 40.7 ± 0.4 | 40.1 ± 0.7 | 41.0 ± 0.5 | 41.5 ± 0.6 | 45.6 ± 0.7** | 45.0 ± 1.0** |
| Day 20 | 43.0 ± 0.5 | 43.0 ± 0.7 | 42.6 ± 0.8 | 43.1 ± 0.5 | 42.9 ± 0.3 | 44.2 ± 0.9 |
| Week 13 | 45.0 ± 0.5 | 45.3 ± 0.7 | 45.4 ± 0.3 | 46.2 ± 0.7 | 46.0 ± 0.3 | 44.6 ± 0.7 |
| Manual hematocrit (%) | | | | | | |
| Day 5 | 39.3 ± 0.4 | 38.6 ± 0.9 | 39.8 ± 0.5 | 40.1 ± 0.7 | 44.2 ± 0.8** | 43.4 ± 1.0** |
| Day 20 | 41.3 ± 0.6 | 42.7 ± 0.7 | 41.8 ± 0.8 | 42.2 ± 0.5 | 41.3 ± 0.4 | 43.5 ± 1.0 |
| Week 13 | 43.5 ± 0.6 | 44.0 ± 0.6 | 44.2 ± 0.2 | 44.7 ± 0.6 | 44.4 ± 0.4 | 43.4 ± 0.6 |
| Hemoglobin (g/dL) | | | | | | |
| Day 5 | 13.3 ± 0.1 | 13.1 ± 0.2 | 13.5 ± 0.2 | 13.7 ± 0.2 | 15.1 ± 0.2** | 14.8 ± 0.3** |
| Day 20 | 14.3 ± 0.2 | 14.2 ± 0.2 | 14.0 ± 0.2 | 14.1 ± 0.2 | 14.0 ± 0.1 | 14.6 ± 0.3 |
| Week 13 | 15.1 ± 0.2 | 15.2 ± 0.2 | 15.2 ± 0.1 | 15.5 ± 0.1 | 15.3 ± 0.1 | 14.8 ± 0.2 |
| Erythrocytes (10 ⁶ /μL) | | | | | | |
| Day 5 | 6.43 ± 0.07 | 6.35 ± 0.10 | 6.43 ± 0.09 | 6.62 ± 0.08 | 7.34 ± 0.16** | 7.13 ± 0.17** |
| Day 20 | 6.99 ± 0.12 | 6.94 ± 0.10 | 6.90 ± 0.12 | 7.04 ± 0.10 | 7.07 ± 0.09 | 7.36 ± 0.13 |
| Week 13 | 8.52 ± 0.14 | 8.59 ± 0.17 | 8.71 ± 0.12 | 8.61 ± 0.14 | 8.64 ± 0.12 | 8.42 ± 0.10 |
| Reticulocytes (10 ⁶ /μL) | | | | | | |
| Day 5 | 0.27 ± 0.02 | 0.29 ± 0.03 | 0.29 ± 0.02 | 0.32 ± 0.02 | 0.27 ± 0.02 | 0.26 ± 0.02 |
| Day 20 | 0.21 ± 0.01 | 0.21 ± 0.01 | 0.18 ± 0.01 | 0.19 ± 0.01 | 0.22 ± 0.02 | 0.23 ± 0.01 |
| Week 13 | 0.13 ± 0.01 | 0.15 ± 0.01 | 0.14 ± 0.01 | 0.16 ± 0.01 | 0.18 ± 0.02 | 0.15 ± 0.01 |
| Nucleated erythrocytes (10 ³ /μL) | | | | | | |
| Day 5 | 0.06 ± 0.02 | 0.02 ± 0.01 | 0.04 ± 0.02 | 0.01 ± 0.01* | 0.02 ± 0.01 | 0.02 ± 0.01 |
| Day 20 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.03 ± 0.02 | 0.03 ± 0.02 | 0.01 ± 0.01 |
| Week 13 | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.03 ± 0.02 | 0.04 ± 0.02 |
| Mean cell volume (fL) | | | | | | |
| Day 5 | 63.5 ± 0.6 | 63.2 ± 0.7 | 63.9 ± 0.7 | 62.6 ± 0.6 | 62.2 ± 0.5 | 63.2 ± 0.7 |
| Day 20 | 61.7 ± 0.7 | 62.1 ± 0.9 | 61.8 ± 0.7 | 61.4 ± 0.6 | 60.7 ± 0.4 | 60.2 ± 0.5 |
| Week 13 | 52.9 ± 0.6 | 52.9 ± 0.5 | 52.4 ± 0.5 | 53.8 ± 0.6 | 53.3 ± 0.7 | 53.2 ± 0.5 |
| Mean cell hemoglobin (pg) | | | | | | |
| Day 5 | 20.8 ± 0.2 | 20.7 ± 0.2 | 21.0 ± 0.2 | 20.6 ± 0.2 | 20.6 ± 0.2 | 20.8 ± 0.2 |
| Day 20 | 20.4 ± 0.2 | 20.5 ± 0.2 | 20.4 ± 0.2 | 20.1 ± 0.2 | 19.8 ± 0.2 | 19.8 ± 0.2* |
| Week 13 | 17.7 ± 0.3 | 17.7 ± 0.2 | 17.5 ± 0.2 | 18.0 ± 0.2 | 17.7 ± 0.2 | 17.6 ± 0.2 |
| Mean cell hemoglobin concentration (g/dL) | | | | | | |
| Day 5 | 32.8 ± 0.1 | 32.7 ± 0.1 | 32.9 ± 0.2 | 32.9 ± 0.2 | 33.1 ± 0.2 | 32.9 ± 0.1 |
| Day 20 | 33.2 ± 0.2 | 33.1 ± 0.3 | 33.0 ± 0.2 | 32.8 ± 0.2 | 32.7 ± 0.1 | 33.0 ± 0.1 |
| Week 13 | 33.5 ± 0.2 | 33.6 ± 0.1 | 33.5 ± 0.2 | 33.5 ± 0.2 | 33.3 ± 0.2 | 33.3 ± 0.1 |
| Platelets (10 ³ /μL) | | | | | | |
| Day 5 | 1,356.5 ± 55.6 | 1,361.6 ± 46.8 | 1,398.8 ± 66.0 | 1,297.1 ± 70.9 | 1,364.3 ± 50.5 | 1,421.5 ± 75.1 |
| Day 20 | 1,227.3 ± 39.0 | 1,227.0 ± 49.9 | 1,225.9 ± 46.1 | 1,177.4 ± 67.6 | 1,207.3 ± 52.1 | 1,258.0 ± 78.4 |
| Week 13 | 1,055.2 ± 89.2 | 993.1 ± 57.2 | 1,012.2 ± 53.8 | 1,040.8 ± 55.8 | 1,232.1 ± 62.4 | 1,047.6 ± 72.7 |
| Leukocytes (10 ³ /μL) | | | | | | |
| Day 5 | 9.82 ± 0.56 | 11.44 ± 0.45 | 9.11 ± 0.94 | 9.29 ± 0.61 | 8.98 ± 0.32 | 9.05 ± 0.84 |
| Day 20 | 10.09 ± 0.61 | 12.41 ± 0.53 | 10.14 ± 0.87 | 9.52 ± 0.35 | 10.16 ± 0.78 | 11.15 ± 0.92 |
| Week 13 | 9.81 ± 0.77 | 10.67 ± 0.88 | 9.89 ± 0.61 | 10.45 ± 0.43 | 11.38 ± 0.47 | 10.81 ± 0.87 |
| Segmented neutrophils (10 ³ /μL) | | | | | | |
| Day 5 | 1.34 ± 0.17 | 1.98 ± 0.27 | 1.39 ± 0.21 | 1.47 ± 0.20 | 1.52 ± 0.14 | 1.26 ± 0.16 |
| Day 20 | 1.46 ± 0.19 | 1.84 ± 0.24 | 1.54 ± 0.14 | 1.29 ± 0.17 | 1.55 ± 0.15 | 2.02 ± 0.34 |
| Week 13 | 1.66 ± 0.17 | 1.52 ± 0.16 | 1.55 ± 0.21 | 1.71 ± 0.14 | 2.08 ± 0.19 | 1.67 ± 0.21 |

TABLE G2
Hematology and Clinical Chemistry Data for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|------------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Hematology (continued) | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 10 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 9 | 9 | 9 | 10 | 10 |
| Week 13 | 10 | 10 | 10 | 10 | 9 | 10 |
| Lymphocytes ($10^3/\mu\text{L}$) | | | | | | |
| Day 5 | 8.41 \pm 0.49 | 9.32 \pm 0.35 | 7.64 \pm 0.78 | 7.70 \pm 0.51 | 7.38 \pm 0.34 | 7.69 \pm 0.86 |
| Day 20 | 8.52 \pm 0.60 | 10.48 \pm 0.62 | 8.51 \pm 0.80 | 8.13 \pm 0.37 | 8.50 \pm 0.66 | 9.01 \pm 0.74 |
| Week 13 | 8.06 \pm 0.72 | 9.06 \pm 0.79 | 8.24 \pm 0.70 | 8.63 \pm 0.42 | 9.19 \pm 0.50 | 9.05 \pm 0.81 |
| Monocytes ($10^3/\mu\text{L}$) | | | | | | |
| Day 5 | 0.04 \pm 0.02 | 0.08 \pm 0.03 | 0.05 \pm 0.03 | 0.09 \pm 0.03 | 0.03 \pm 0.01 | 0.04 \pm 0.02 |
| Day 20 | 0.08 \pm 0.03 | 0.08 \pm 0.03 | 0.07 \pm 0.02 | 0.07 \pm 0.02 | 0.05 \pm 0.02 | 0.09 \pm 0.02 |
| Week 13 | 0.03 \pm 0.02 | 0.05 \pm 0.03 | 0.03 \pm 0.02 | 0.03 \pm 0.02 | 0.06 \pm 0.03 | 0.07 \pm 0.02 |
| Basophils ($10^3/\mu\text{L}$) | | | | | | |
| Day 5 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 |
| Day 20 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 |
| Week 13 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 | 0.000 \pm 0.000 |
| Eosinophils ($10^3/\mu\text{L}$) | | | | | | |
| Day 5 | 0.03 \pm 0.02 | 0.06 \pm 0.03 | 0.03 \pm 0.02 | 0.03 \pm 0.03 | 0.05 \pm 0.02 | 0.06 \pm 0.03 |
| Day 20 | 0.03 \pm 0.02 | 0.01 \pm 0.01 | 0.03 \pm 0.02 | 0.03 \pm 0.02 | 0.06 \pm 0.03 | 0.04 \pm 0.02 |
| Week 13 | 0.06 \pm 0.02 | 0.05 \pm 0.02 | 0.07 \pm 0.03 | 0.09 \pm 0.04 | 0.05 \pm 0.03 | 0.02 \pm 0.01 |
| Clinical Chemistry | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 10 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| Week 13 | 10 | 10 | 10 | 10 | 9 | 10 |
| Urea nitrogen (mg/dL) | | | | | | |
| Day 5 | 19.9 \pm 0.8 | 19.4 \pm 0.6 | 18.4 \pm 1.0 | 18.9 \pm 1.0 | 23.1 \pm 1.1* | 25.2 \pm 1.3** |
| Day 20 | 23.3 \pm 0.9 | 24.5 \pm 0.5 | 22.7 \pm 0.6 | 25.6 \pm 1.0 | 25.8 \pm 0.6* | 28.0 \pm 1.1** |
| Week 13 | 28.1 \pm 0.8 | 27.5 \pm 0.9 | 27.0 \pm 1.0 | 26.8 \pm 1.7 | 31.2 \pm 1.8 | 29.7 \pm 2.3 |
| Creatinine (mg/dL) | | | | | | |
| Day 5 | 0.50 \pm 0.03 | 0.52 \pm 0.02 | 0.46 \pm 0.02 | 0.48 \pm 0.02 | 0.53 \pm 0.03 | 0.52 \pm 0.01 |
| Day 20 | 0.54 \pm 0.02 | 0.53 \pm 0.02 | 0.54 \pm 0.02 | 0.53 \pm 0.05 | 0.57 \pm 0.02 | 0.57 \pm 0.04 |
| Week 13 | 0.62 \pm 0.04 | 0.68 \pm 0.02 | 0.68 \pm 0.02 | 0.72 \pm 0.03 | 0.74 \pm 0.04 | 0.67 \pm 0.03 |
| Total protein (g/dL) | | | | | | |
| Day 5 | 5.9 \pm 0.1 | 5.8 \pm 0.1 | 5.8 \pm 0.1 | 5.9 \pm 0.1 | 5.8 \pm 0.1 | 6.1 \pm 0.2 |
| Day 20 | 6.5 \pm 0.1 | 6.7 \pm 0.1 | 6.4 \pm 0.1 | 6.8 \pm 0.1 | 6.7 \pm 0.1 | 6.7 \pm 0.1 |
| Week 13 | 6.6 \pm 0.1 | 6.7 \pm 0.1 | 6.7 \pm 0.1 | 7.0 \pm 0.1 | 6.9 \pm 0.1 | 6.6 \pm 0.1 |
| Albumin (g/dL) | | | | | | |
| Day 5 | 3.0 \pm 0.0 | 3.2 \pm 0.1 | 3.1 \pm 0.0 | 3.2 \pm 0.1 | 3.2 \pm 0.1 | 3.3 \pm 0.1* |
| Day 20 | 3.3 \pm 0.1 | 3.4 \pm 0.1 | 3.3 \pm 0.1 | 3.5 \pm 0.0 | 3.4 \pm 0.1 | 3.4 \pm 0.1 |
| Week 13 | 3.6 \pm 0.1 | 3.8 \pm 0.1 | 3.8 \pm 0.1 | 3.9 \pm 0.1* | 3.8 \pm 0.1 | 3.8 \pm 0.1 |
| Alanine aminotransferase (IU/L) | | | | | | |
| Day 5 | 52 \pm 2 | 53 \pm 2 | 52 \pm 2 | 53 \pm 4 | 117 \pm 30** | 134 \pm 74 |
| Day 20 | 48 \pm 2 | 43 \pm 1 | 45 \pm 2 | 45 \pm 2 | 45 \pm 2 | 299 \pm 162 |
| Week 13 | 54 \pm 2 | 51 \pm 4 | 50 \pm 3 | 47 \pm 3 | 146 \pm 51 | 62 \pm 11 |
| Alkaline phosphatase (IU/L) | | | | | | |
| Day 5 | 339 \pm 13 | 343 \pm 19 | 327 \pm 20 | 303 \pm 26 | 339 \pm 29 | 378 \pm 30 |
| Day 20 | 294 \pm 11 | 281 \pm 21 | 268 \pm 16 | 229 \pm 16* | 262 \pm 19 | 288 \pm 30 |
| Week 13 | 179 \pm 7 | 189 \pm 8 | 160 \pm 7 | 157 \pm 6* | 168 \pm 18 | 143 \pm 11* |

TABLE G2
Hematology and Clinical Chemistry Data for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|--------------------------------|--------------|------------|--------------|---------------|----------------|----------------|
| Clinical Chemistry (continued) | | | | | | |
| n | | | | | | |
| Day 5 | 10 | 10 | 10 | 10 | 10 | 10 |
| Day 20 | 10 | 10 | 10 | 10 | 10 | 10 |
| Week 13 | 10 | 10 | 10 | 10 | 9 | 10 |
| Creatine kinase (U/L) | | | | | | |
| Day 5 | 242 ± 23 | 211 ± 22 | 280 ± 31 | 255 ± 21 | 306 ± 35 | 291 ± 51 |
| Day 20 | 223 ± 42 | 322 ± 69 | 345 ± 80 | 298 ± 56 | 333 ± 91 | 362 ± 99 |
| Week 13 | 274 ± 65 | 454 ± 136 | 290 ± 45 | 272 ± 58 | 331 ± 64 | 309 ± 56 |
| Sorbitol dehydrogenase (IU/L) | | | | | | |
| Day 5 | 8 ± 1 | 8 ± 1 | 7 ± 1 | 7 ± 0 | 615 ± 179** | 370 ± 289** |
| Day 20 | 7 ± 0 | 7 ± 1 | 7 ± 1 | 8 ± 1 | 9 ± 1 | 1,075 ± 605** |
| Week 13 | 7 ± 0 | 8 ± 1 | 7 ± 1 | 9 ± 1 | 253 ± 94** | 49 ± 29** |
| Bile acids (μmol/L) | | | | | | |
| Day 5 | 100.0 ± 14.8 | 77.4 ± 8.4 | 118.5 ± 12.6 | 119.1 ± 16.9 | 235.0 ± 44.4** | 191.3 ± 27.9** |
| Day 20 | 70.2 ± 8.1 | 76.0 ± 8.4 | 98.0 ± 14.9 | 159.1 ± 41.2* | 111.5 ± 23.3 | 172.4 ± 37.9* |
| Week 13 | 75.5 ± 13.9 | 66.7 ± 6.7 | 67.4 ± 6.3 | 64.1 ± 8.1 | 117.8 ± 24.9 | 116.3 ± 20.2 |

* Significantly different (P#0.05) from the control group by Dunn's or Shirley's test

** P#0.01

^a Mean ± standard error. Statistical tests were performed on unrounded data.

APPENDIX H

ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

| | | |
|-----------------|--|------------|
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TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|------------------|----------------|----------------|-----------------|-----------------|-----------------|-----------------|
| Male | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 335 ± 9 | 334 ± 7 | 337 ± 6 | 334 ± 7 | 316 ± 5 | 287 ± 5** |
| Heart | | | | | | |
| Absolute | 1.145 ± 0.034 | 1.187 ± 0.049 | 1.140 ± 0.038 | 1.140 ± 0.029 | 1.129 ± 0.059 | 1.159 ± 0.037 |
| Relative | 3.42 ± 0.08 | 3.56 ± 0.13 | 3.38 ± 0.08 | 3.42 ± 0.08 | 3.57 ± 0.17 | 4.04 ± 0.12** |
| R. Kidney | | | | | | |
| Absolute | 1.352 ± 0.037 | 1.333 ± 0.039 | 1.345 ± 0.032 | 1.398 ± 0.040 | 1.381 ± 0.026 | 1.396 ± 0.037 |
| Relative | 4.04 ± 0.05 | 3.99 ± 0.06 | 3.99 ± 0.05 | 4.18 ± 0.08 | 4.38 ± 0.08** | 4.87 ± 0.08** |
| Liver | | | | | | |
| Absolute | 14.384 ± 0.601 | 14.901 ± 0.579 | 15.415 ± 0.429 | 16.091 ± 0.541* | 16.535 ± 0.295* | 15.512 ± 0.500* |
| Relative | 42.81 ± 0.99 | 44.52 ± 0.77 | 45.75 ± 0.76* | 48.07 ± 0.81** | 52.41 ± 0.99** | 54.06 ± 1.27** |
| Lung | | | | | | |
| Absolute | 1.837 ± 0.061 | 1.782 ± 0.048 | 1.791 ± 0.050 | 1.844 ± 0.077 | 1.747 ± 0.051 | 1.558 ± 0.053** |
| Relative | 5.49 ± 0.16 | 5.36 ± 0.17 | 5.33 ± 0.17 | 5.51 ± 0.18 | 5.55 ± 0.20 | 5.43 ± 0.16 |
| R. Testis | | | | | | |
| Absolute | 1.502 ± 0.026 | 1.474 ± 0.020 | 1.486 ± 0.025 | 1.502 ± 0.019 | 1.516 ± 0.013 | 1.437 ± 0.019 |
| Relative | 4.51 ± 0.15 | 4.43 ± 0.10 | 4.42 ± 0.08 | 4.50 ± 0.05 | 4.81 ± 0.07* | 5.02 ± 0.08** |
| Thymus | | | | | | |
| Absolute | 0.320 ± 0.022 | 0.363 ± 0.031 | 0.352 ± 0.020 | 0.350 ± 0.018 | 0.362 ± 0.026 | 0.294 ± 0.023 |
| Relative | 0.95 ± 0.06 | 1.08 ± 0.07 | 1.04 ± 0.05 | 1.05 ± 0.04 | 1.15 ± 0.08 | 1.03 ± 0.08 |
| Female | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 8 |
| Necropsy body wt | 198 ± 3 | 196 ± 4 | 195 ± 2 | 197 ± 4 | 185 ± 2** | 180 ± 3** |
| Heart | | | | | | |
| Absolute | 0.807 ± 0.033 | 0.752 ± 0.027 | 0.797 ± 0.030 | 0.786 ± 0.033 | 0.806 ± 0.029 | 0.767 ± 0.054 |
| Relative | 4.07 ± 0.16 | 3.83 ± 0.11 | 4.10 ± 0.17 | 3.99 ± 0.15 | 4.37 ± 0.18 | 4.26 ± 0.30 |
| R. Kidney | | | | | | |
| Absolute | 0.752 ± 0.017 | 0.731 ± 0.018 | 0.741 ± 0.008 | 0.795 ± 0.012 | 0.774 ± 0.019 | 0.739 ± 0.024 |
| Relative | 3.80 ± 0.09 | 3.74 ± 0.10 | 3.81 ± 0.06 | 4.04 ± 0.05 | 4.19 ± 0.11** | 4.10 ± 0.10* |
| Liver | | | | | | |
| Absolute | 6.866 ± 0.135 | 7.305 ± 0.133 | 7.874 ± 0.212** | 8.732 ± 0.244** | 9.391 ± 0.152** | 9.619 ± 0.293** |
| Relative | 34.68 ± 0.53 | 37.32 ± 0.76 | 40.46 ± 1.23** | 44.30 ± 0.82** | 50.80 ± 0.75** | 53.44 ± 1.79** |
| Lung | | | | | | |
| Absolute | 1.277 ± 0.049 | 1.230 ± 0.048 | 1.253 ± 0.070 | 1.289 ± 0.059 | 1.290 ± 0.034 | 1.173 ± 0.022 |
| Relative | 6.46 ± 0.27 | 6.26 ± 0.15 | 6.45 ± 0.40 | 6.53 ± 0.22 | 6.98 ± 0.16 | 6.51 ± 0.07 |
| Thymus | | | | | | |
| Absolute | 0.265 ± 0.011 | 0.295 ± 0.013 | 0.280 ± 0.008 | 0.305 ± 0.037 | 0.313 ± 0.034 | 0.252 ± 0.011 |
| Relative | 1.34 ± 0.06 | 1.50 ± 0.06 | 1.44 ± 0.04 | 1.54 ± 0.18 | 1.70 ± 0.19 | 1.39 ± 0.05 |

* Significantly different (P#0.05) from the control group by Williams' or Dunnett's test

** P#0.01

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine^a

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| n | 10 | 10 | 10 | 10 | 9 | 10 |
| Necropsy body wt | 490 ± 10 | 457 ± 12 | 469 ± 6 | 445 ± 17* | 428 ± 8** | 405 ± 15** |
| Heart | | | | | | |
| Absolute | 1.679 ± 0.043 | 1.730 ± 0.088 | 1.780 ± 0.051 | 1.712 ± 0.090 | 1.560 ± 0.081 | 1.513 ± 0.071 |
| Relative | 3.44 ± 0.09 | 3.78 ± 0.14 | 3.80 ± 0.13 | 3.84 ± 0.10 | 3.63 ± 0.13 | 3.74 ± 0.12 |
| R. Kidney | | | | | | |
| Absolute | 1.948 ± 0.069 | 1.924 ± 0.061 | 2.004 ± 0.046 | 2.085 ± 0.079 | 2.041 ± 0.115 | 1.998 ± 0.114 |
| Relative | 3.98 ± 0.11 | 4.21 ± 0.09 | 4.27 ± 0.10 | 4.70 ± 0.13** | 4.76 ± 0.21** | 4.92 ± 0.19** |
| Liver | | | | | | |
| Absolute | 20.949 ± 0.624 | 21.152 ± 0.840 | 21.528 ± 0.608 | 21.706 ± 0.945 | 22.662 ± 1.098 | 21.367 ± 1.160 |
| Relative | 42.79 ± 0.98 | 46.33 ± 1.47 | 45.90 ± 1.25 | 48.78 ± 0.97** | 52.77 ± 1.68** | 52.60 ± 1.65** |
| Lung | | | | | | |
| Absolute | 2.534 ± 0.090 | 2.366 ± 0.129 | 2.429 ± 0.098 | 2.217 ± 0.104 | 2.133 ± 0.134 | 2.213 ± 0.111 |
| Relative | 5.22 ± 0.28 | 5.16 ± 0.20 | 5.20 ± 0.25 | 5.00 ± 0.19 | 4.97 ± 0.25 | 5.46 ± 0.19 |
| R. Testis | | | | | | |
| Absolute | 1.737 ± 0.046 | 1.632 ± 0.074 | 1.843 ± 0.039 | 1.731 ± 0.051 | 1.939 ± 0.181 | 1.823 ± 0.085 |
| Relative | 3.56 ± 0.14 | 3.59 ± 0.17 | 3.93 ± 0.09 | 3.92 ± 0.12 | 4.50 ± 0.34** | 4.52 ± 0.18** |
| Thymus | | | | | | |
| Absolute | 0.479 ± 0.039 | 0.501 ± 0.035 | 0.458 ± 0.026 | 0.499 ± 0.036 | 0.423 ± 0.029 | 0.507 ± 0.061 |
| Relative | 0.98 ± 0.08 | 1.11 ± 0.09 | 0.98 ± 0.06 | 1.12 ± 0.07 | 0.99 ± 0.06 | 1.23 ± 0.12 |

* Significantly different (P#0.05) from the control group by Williams' or Dunnett's test

** P#0.01

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE H3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Drinking Water Study of Pyridine^a

| | 0 ppm | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|------------------|---------------|----------------|----------------|----------------------------|-----------------|-----------------|
| Male | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 38.9 ± 0.8 | 37.6 ± 1.1 | 38.8 ± 0.9 | 39.6 ± 1.2 | 38.8 ± 0.8 | 36.9 ± 0.7 |
| Heart | | | | | | |
| Absolute | 0.199 ± 0.008 | 0.193 ± 0.010 | 0.211 ± 0.013 | 0.203 ± 0.010 | 0.188 ± 0.006 | 0.193 ± 0.008 |
| Relative | 5.12 ± 0.17 | 5.15 ± 0.26 | 5.41 ± 0.28 | 5.11 ± 0.19 | 4.85 ± 0.14 | 5.25 ± 0.19 |
| R. Kidney | | | | | | |
| Absolute | 0.304 ± 0.007 | 0.291 ± 0.010 | 0.302 ± 0.016 | 0.293 ± 0.011 | 0.254 ± 0.009* | 0.274 ± 0.008* |
| Relative | 7.85 ± 0.24 | 7.76 ± 0.16 | 7.80 ± 0.43 | 7.41 ± 0.23 | 6.57 ± 0.26** | 7.44 ± 0.24 |
| Liver | | | | | | |
| Absolute | 1.855 ± 0.044 | 1.878 ± 0.048 | 2.058 ± 0.057* | 2.177 ± 0.083** | 2.264 ± 0.066** | 2.249 ± 0.067** |
| Relative | 47.81 ± 1.21 | 50.16 ± 1.06 | 53.08 ± 1.19** | 54.85 ± 0.76** | 58.36 ± 1.23** | 60.96 ± 1.01** |
| Lung | | | | | | |
| Absolute | 0.281 ± 0.020 | 0.267 ± 0.017 | 0.293 ± 0.022 | 0.274 ± 0.018 ^b | 0.288 ± 0.017 | 0.269 ± 0.008 |
| Relative | 7.31 ± 0.66 | 7.13 ± 0.44 | 7.54 ± 0.48 | 6.85 ± 0.41 ^b | 7.46 ± 0.47 | 7.36 ± 0.33 |
| R. Testis | | | | | | |
| Absolute | 0.125 ± 0.003 | 0.125 ± 0.004 | 0.127 ± 0.004 | 0.129 ± 0.004 | 0.123 ± 0.002 | 0.117 ± 0.004 |
| Relative | 3.22 ± 0.10 | 3.34 ± 0.07 | 3.27 ± 0.12 | 3.27 ± 0.10 | 3.18 ± 0.06 | 3.18 ± 0.12 |
| Thymus | | | | | | |
| Absolute | 0.057 ± 0.007 | 0.059 ± 0.005 | 0.065 ± 0.007 | 0.057 ± 0.009 | 0.055 ± 0.005 | 0.047 ± 0.006 |
| Relative | 1.46 ± 0.17 | 1.59 ± 0.16 | 1.65 ± 0.17 | 1.42 ± 0.18 | 1.42 ± 0.13 | 1.28 ± 0.14 |
| Female | | | | | | |
| n | 10 | 10 | 10 | 9 | 10 | 10 |
| Necropsy body wt | 33.0 ± 1.1 | 37.1 ± 1.1 | 33.9 ± 0.9 | 34.0 ± 1.1 | 32.9 ± 0.9 | 29.4 ± 0.9* |
| Heart | | | | | | |
| Absolute | 0.146 ± 0.007 | 0.157 ± 0.006 | 0.139 ± 0.003 | 0.134 ± 0.006 | 0.141 ± 0.006 | 0.129 ± 0.003* |
| Relative | 4.45 ± 0.24 | 4.27 ± 0.21 | 4.13 ± 0.17 | 3.93 ± 0.10 | 4.28 ± 0.14 | 4.40 ± 0.12 |
| R. Kidney | | | | | | |
| Absolute | 0.199 ± 0.006 | 0.219 ± 0.004 | 0.193 ± 0.010 | 0.203 ± 0.007 | 0.206 ± 0.004 | 0.204 ± 0.005 |
| Relative | 6.07 ± 0.14 | 5.94 ± 0.14 | 5.73 ± 0.32 | 5.97 ± 0.12 | 6.28 ± 0.14 | 6.98 ± 0.19** |
| Liver | | | | | | |
| Absolute | 1.513 ± 0.039 | 1.766 ± 0.039* | 1.630 ± 0.044 | 1.743 ± 0.081* | 1.836 ± 0.059** | 1.609 ± 0.071 |
| Relative | 46.04 ± 1.09 | 47.80 ± 0.84 | 48.29 ± 1.67 | 51.04 ± 1.20** | 55.71 ± 0.81** | 54.69 ± 1.58** |
| Lung | | | | | | |
| Absolute | 0.263 ± 0.016 | 0.268 ± 0.015 | 0.224 ± 0.008 | 0.233 ± 0.009 | 0.252 ± 0.012 | 0.231 ± 0.012 |
| Relative | 7.98 ± 0.44 | 7.25 ± 0.41 | 6.60 ± 0.24* | 6.90 ± 0.35 | 7.66 ± 0.32 | 7.91 ± 0.46 |
| Thymus | | | | | | |
| Absolute | 0.062 ± 0.005 | 0.068 ± 0.004 | 0.060 ± 0.005 | 0.065 ± 0.005 | 0.056 ± 0.003 | 0.055 ± 0.003 |
| Relative | 1.87 ± 0.12 | 1.85 ± 0.12 | 1.78 ± 0.13 | 1.91 ± 0.15 | 1.72 ± 0.12 | 1.89 ± 0.10 |

* Significantly different (P#0.05) from the control group by Williams' or Dunnett's test

** P#0.01

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

^b n=9

APPENDIX I

REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

| | | |
|-----------------|---|------------|
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TABLE I1
Summary of Reproductive Tissue Evaluations for Male F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|---|---------------------------|---------------------------|-----------------|-------------------|
| n | 10 | 10 | 10 | 10 |
| Weights (g) | | | | |
| Necropsy body wt | 339 ± 9 | 334 ± 7 | 316 ± 5* | 287 ± 5** |
| L. cauda epididymis | 0.1834 ± 0.0057 | 0.1866 ± 0.0040 | 0.1939 ± 0.0039 | 0.1785 ± 0.0042 |
| L. epididymis | 0.4590 ± 0.0105 | 0.4529 ± 0.0037 | 0.4723 ± 0.0030 | 0.4201 ± 0.0068** |
| L. testis | 1.5272 ± 0.0165 | 1.5036 ± 0.0181 | 1.5726 ± 0.0150 | 1.4368 ± 0.0125** |
| Spermatid measurements | | | | |
| Spermatid heads (10 ⁷ /g testis) | 11.29 ± 0.72 ^b | 10.86 ± 0.41 ^b | 10.87 ± 0.35 | 11.36 ± 0.37 |
| Spermatid heads (10 ⁷ /testis) | 17.29 ± 1.17 ^b | 16.31 ± 0.60 ^b | 17.07 ± 0.49 | 16.33 ± 0.58 |
| Spermatid count (mean/10 ¹⁴ mL suspension) | 86.47 ± 5.84 ^b | 81.53 ± 3.01 ^b | 85.33 ± 2.44 | 81.63 ± 2.88 |
| Epididymal spermatozoal measurements | | | | |
| Motility (%) | 98.89 ± 0.19 | 98.96 ± 0.16 | 99.00 ± 0.13 | 98.87 ± 0.15 |
| Concentration (10 ⁶ /g cauda epididymal tissue) | 748 ± 34 | 733 ± 24 | 683 ± 18 | 714 ± 36 |

* Significantly different (P#0.05) from the control group by Williams' test

** Significantly different (P#0.01) from the control group by Williams' test (body weights) or Dunnett's test (epididymal and testis weights)

^a Data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (caudal weight) or

Dunn's test (spermatid and epididymal spermatozoal measurements).

^b n=9

TABLE I2
Summary of Estrous Cycle Characterization for Female F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|-----------------------------|--------------------------|-------------|-------------|----------------------------|
| n | 10 | 10 | 10 | 8 |
| Necropsy body wt (g) | 198 ± 3 | 197 ± 4 | 185 ± 2** | 180 ± 3** |
| Estrous cycle length (days) | 5.00 ± 0.00 ^b | 5.00 ± 0.00 | 5.30 ± 0.30 | 6.08 ± 0.30** ^c |
| Estrous stages (% of cycle) | | | | |
| Diestrus | 42.5 | 45.8 | 40.8 | 54.2 |
| Proestrus | 13.3 | 16.7 | 16.7 | 12.5 |
| Estrus | 25.0 | 19.2 | 23.3 | 19.8 |
| Metestrus | 19.2 | 18.3 | 19.2 | 13.5 |

** Significantly different (P#0.01) from the control group by Williams' test (body weights) or Shirley's test (estrous cycle length)

^a Necropsy body weight and estrous cycle length data are presented as mean ± standard error. By multivariate analysis of variance, exposed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.

^b Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

^c Estrous cycle was longer than 12 days or unclear in 2 of 8 animals.

TABLE I3
Summary of Reproductive Tissue Evaluations for Male Mice in the 13-Week Drinking Water Study of Pyridine^a

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|---|-----------------|-----------------|-----------------|-----------------|
| n | 10 | 10 | 10 | 10 |
| Weights (g) | | | | |
| Necropsy body wt | 38.9 ± 0.8 | 39.6 ± 1.2 | 38.8 ± 0.8 | 36.9 ± 0.7 |
| L. cauda epididymis | 0.0170 ± 0.0011 | 0.0166 ± 0.0006 | 0.0170 ± 0.0008 | 0.0155 ± 0.0008 |
| L. epididymis | 0.0453 ± 0.0018 | 0.0480 ± 0.0016 | 0.0449 ± 0.0017 | 0.0446 ± 0.0019 |
| L. testis | 0.1174 ± 0.0036 | 0.1181 ± 0.0034 | 0.1169 ± 0.0033 | 0.1088 ± 0.0044 |
| Spermatid measurements | | | | |
| Spermatid heads (10 ⁷ /g testis) | 15.81 ± 0.62 | 13.37 ± 0.56 | 15.53 ± 1.05 | 14.73 ± 1.10 |
| Spermatid heads (10 ⁷ /testis) | 1.85 ± 0.09 | 1.57 ± 0.05* | 1.80 ± 0.11 | 1.61 ± 0.14 |
| Spermatid count (mean/10 ¹ ± 4 mL suspension) | 57.90 ± 2.69 | 49.00 ± 1.69* | 56.28 ± 3.37 | 50.45 ± 4.26 |
| Epididymal spermatozoal measurements | | | | |
| Motility (%) | 99.31 ± 0.13 | 98.58 ± 0.12** | 98.16 ± 0.26** | 97.21 ± 0.42** |
| Concentration (10 ⁶ /g cauda epididymal tissue) | 1,630 ± 126 | 1,432 ± 57 | 1,360 ± 54 | 1,461 ± 72 |

* Significantly different (P#0.05) from the control group by Dunn's test

** Significantly different (P#0.01) from the control group by Shirley's test

^a Data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (body and tissue weights) or Dunn's test (spermatid heads per gram testis and epididymal spermatozoal concentration).

TABLE I4
Summary of Estrous Cycle Characterization for Female Mice in the 13-Week Drinking Water Study of Pyridine^a

| | 0 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|-----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| n | 10 | 9 | 10 | 10 |
| Necropsy body wt (g) | 33.0 ± 1.1 | 34.0 ± 1.1 | 32.9 ± 0.9 | 29.4 ± 0.9* |
| Estrous cycle length (days) | 4.72 ± 0.55 ^b | 4.50 ± 0.16 ^c | 4.72 ± 0.22 ^b | 4.28 ± 0.15 ^b |
| Estrous stages (% of cycle) | | | | |
| Diestrus | 36.7 | 35.2 | 31.7 | 31.7 |
| Proestrus | 20.0 | 13.9 | 17.5 | 20.0 |
| Estrus | 25.0 | 35.2 | 35.8 | 27.5 |
| Metestrus | 18.3 | 15.7 | 15.0 | 20.8 |

* Significantly different (P#0.05) from the control group by Dunnett's test

^a Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.

^b Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

^c Estrous cycle was longer than 12 days or unclear in 1 of 9 animals.

APPENDIX J

DETERMINATIONS OF PYRIDINE IN PLASMA

| | | |
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TABLE J1
Plasma Concentrations of Pyridine in F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

| | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|-----------------------|-----------------|-----------------|----------------|----------------|----------------|
| Male | | | | | |
| n | 10 ^b | 10 ^c | 9 ^d | 9 | 10 |
| Concentration (µg/mL) | 0.045 ± 0.016 | 0.018 ± 0.007 | 0.084 ± 0.022 | 4.760 ± 1.334 | 38.140 ± 4.173 |
| Female | | | | | |
| n | 10 ^e | 10 ^e | 10 | 10 | 8 |
| Concentration (µg/mL) | 0.057 ± 0.014 | 0.075 ± 0.019 | 2.851 ± 0.602 | 14.810 ± 1.682 | 28.351 ± 5.070 |

^a Mean ± standard error; the minimum detection limit (MDL) was calculated to be 0.009 µg/mL. A value of 0 was used for samples with a concentration below the MDL.

^b Three samples were less than the MDL.

^c Five samples were less than the MDL.

^d One sample was less than the MDL.

^e Two samples were less than the MDL.

TABLE J2
Plasma Concentrations of Pyridine in Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine^a

| | 50 ppm | 100 ppm | 250 ppm | 500 ppm | 1,000 ppm |
|-----------------------|-----------------|----------------|----------------|---------------|----------------|
| n | 10 ^b | 9 ^c | 9 ^d | 9 | 9 |
| Concentration (µg/mL) | 0.153 ± 0.096 | 0.043 ± 0.010 | 2.811 ± 1.406 | 8.278 ± 1.716 | 22.602 ± 5.798 |

^a Mean ± standard error; the minimum detection limit (MDL) was calculated to be 0.009 µg/mL. A value of 0 was used for samples with a concentration below the MDL.

^b Five samples were less than the MDL.

^c Two samples were less than the MDL.

^d One sample was less than the MDL.

APPENDIX K

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF PYRIDINE

Pyridine was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (00103BV), which was used during the 13-week and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the pyridine studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear colorless liquid, was identified as pyridine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra (*Sadtler Standard Spectra*) of pyridine. The infrared and nuclear magnetic spectra are presented in Figures K1 and K2.

The purity of lot 00103BV was determined by elemental analyses, Karl Fischer water analysis, functional group titration, and gas chromatography. For amine group titration, the sample was dissolved in glacial acetic acid, then titrated with 0.1 N perchloric acid in glacial acetic acid to a potentiometric endpoint. The titration was monitored with a combination mV/pH electrode filled with aqueous 3 M potassium chloride. Gas chromatography was performed using a flame ionization detector. Two systems were used:

- A) 10% Carbowax 20M-TPA on 80/100 Chromosorb W AW glass column, with an isothermal oven temperature of 93E C, an oven temperature program of 60E C for 6 minutes, then 60E to 220E C at 10E C per minute, and a nitrogen carrier gas at a flow rate of 70 mL/minute, and
- B) DB-5 Capillary fused silica column, with an oven temperature program of 50E C for 5 minutes, then 50E to 250E C at 10E C per minute, and a helium carrier gas at a flow rate of 5 mL/minute.

Elemental analyses for hydrogen and nitrogen were in agreement with the theoretical values for pyridine; results for carbon were slightly low. Karl Fischer water analysis indicated $0.049\% \pm 0.003\%$ water. Functional group titration indicated a purity of $99.8\% \pm 0.6\%$. Gas chromatography using systems A and B indicated one major peak and no impurities with an area greater than or equal to 0.1% relative to the major peak area. Concomitant analyses of lot 00103BV with lot 18400080202, a previously analyzed lot that was not used in the current studies, were performed with gas chromatography by system A but with an isothermal oven temperature of 95E C and with *n*-butanol as an internal standard. Results indicated a purity of $99.9\% \pm 0.7\%$ for lot 00103BV relative to lot 18400080202. The overall purity of lot 00103BV was determined to be greater than 99%.

The analytical chemistry laboratory conducted bulk stability studies on lot 18400080202 with gas chromatography. A flame ionization detector was used with a 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport glass column, a nitrogen carrier gas at a flow rate of 70 mL/minute, an oven temperature of 50E C, and a 0.4% ethyl acetate internal standard. Samples stored for 2 weeks at 25E or 60E C showed some decomposition. To ensure stability, the bulk chemical was stored at 1E to 7E C (13-week studies) or 2E to 8E C (2-year studies) in amber glass bottles in the dark. Stability was monitored during the studies using gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared as needed by mixing pyridine with deionized water (Table K1). Formulations were stored in Teflon®-capped amber glass bottles (13-week studies) or glass carboys (2-year studies) at room temperature in the dark for up to 3 weeks.

Stability studies of a 0.01 mg/mL formulation were performed by the analytical chemistry laboratory using high-performance liquid chromatography with a Waters μ Bondapak C18 column, ultraviolet (254 nm) detection, a solvent system of 0.005 M triethanolamine in water:methanol (30:70) with the pH adjusted to 7.0 with 10% phosphoric acid, and a flow rate of 1 mL/minute. The stability of the dose formulation was confirmed for at least 3 weeks when stored in the dark at room temperature. Solutions stored at room temperature exposed to air and light were also stable for 96 hours. In an earlier study by the analytical chemistry laboratory, the stability of a 19.64 mg/mL formulation was tested by gas chromatography using flame ionization detection, a 10% Carbowax 20 M/2% KOH on 80/100 mesh Chromosorb W AW silenized glass column, a nitrogen carrier gas at 25 mL/minute, and an oven temperature of 80E C. Stability was confirmed for 7 days at room temperature.

Periodic analyses of the dose formulations of pyridine were conducted at the study laboratory and the analytical chemistry laboratory using HPLC. For the 13-week studies, dose formulations were analyzed after preparation at the beginning, midpoint, and end of the studies (Table K2). During the 2-year studies, dose formulations were analyzed approximately every 6 to 10 weeks (Table K3). All 45 dose formulations analyzed and used during the 13-week studies were within 10% of the target concentration; 44 of 45 animal room samples were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory during the 13-week studies agreed with the results obtained by the study laboratory (Table K4). During the 2-year studies, 191 of 192 of the dose formulations analyzed were within 10% of the target concentration. One formulation was 47% less than the target concentration; because records indicated that the proper amounts of pyridine and deionized water were used, it is possible that the wrong dose formulation was sampled for analysis. This dose formulation was remixed, and the remix was found to be within 10% of the target concentration. All 69 animal room samples were within 10% of the target concentration.

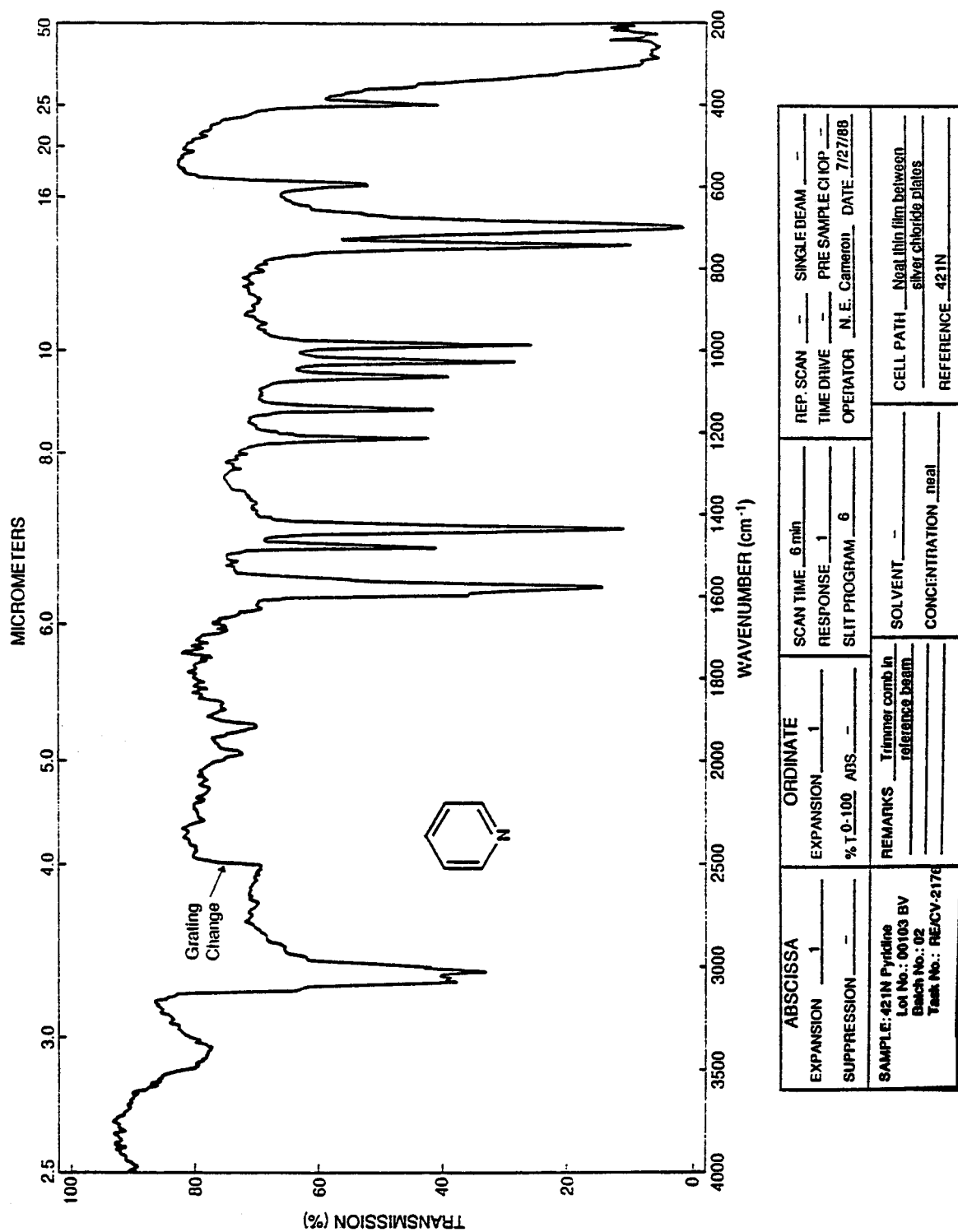


FIGURE K1
Infrared Absorption Spectrum of Pyridine

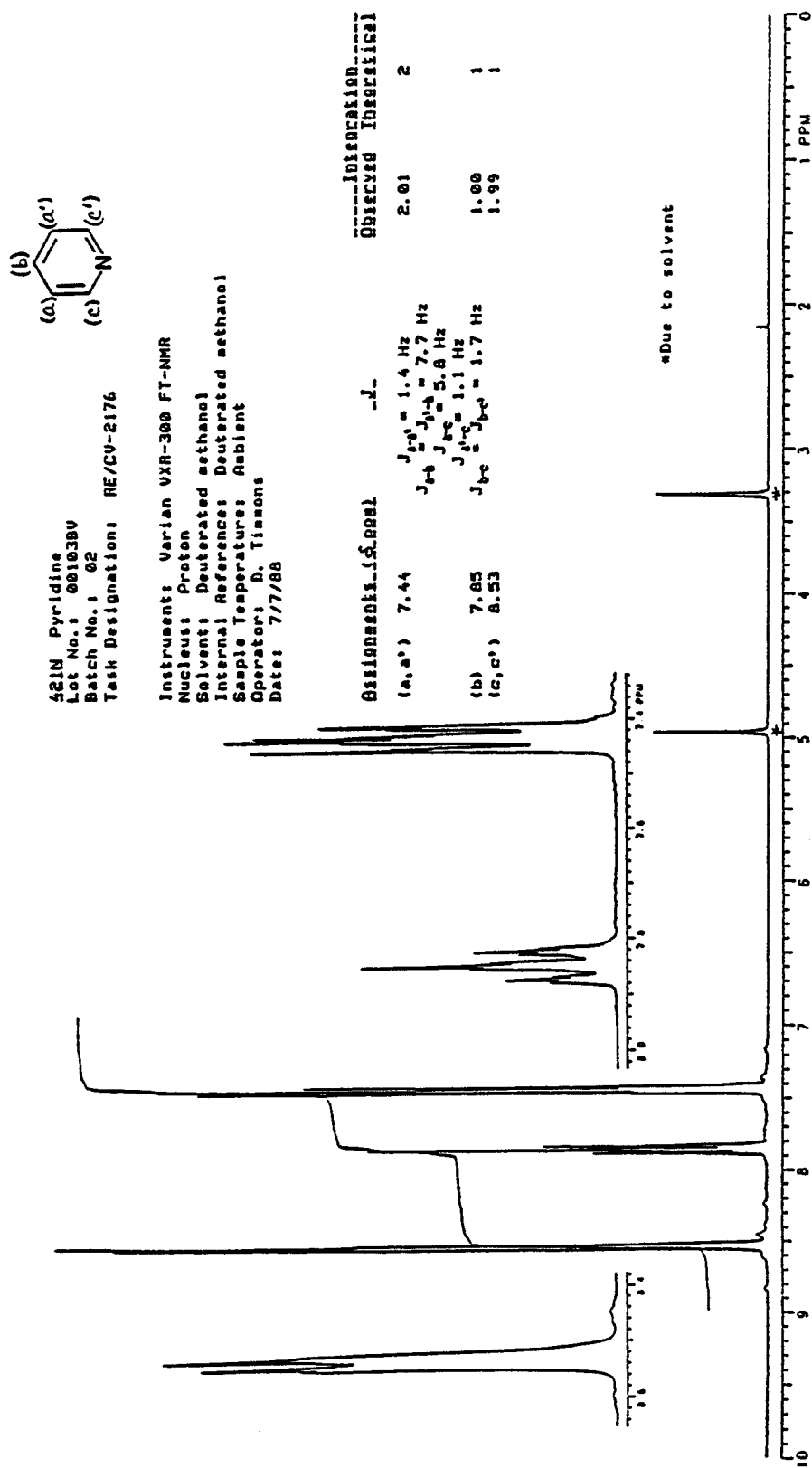


FIGURE K2
Nuclear Magnetic Resonance Spectrum of Pyridine

TABLE K1
Preparation and Storage of Dose Formulations in the Drinking Water Studies of Pyridine

| 13-Week Studies | 2-Year Studies |
|---|--|
| Preparation Dose formulations were prepared as needed by combining weighed amounts of pyridine at room temperature and deionized water, then diluting to volume with additional water and mixing. | Same as 13-week studies |
| Chemical Lot Number 00103BV | 00103BV |
| Maximum Storage Time 3 weeks | 3 weeks |
| Storage Conditions Stored in sealed Teflon®-capped, amber glass bottles at room temperature in the dark | Stored in sealed glass carboys at room temperature in the dark |
| Study Laboratory TSI Mason Research Institute (Worcester, MA) | TSI Mason Laboratories (Worcester, MA) |
| Referee Laboratory Midwest Research Institute (Kansas City, MO) | None performed |

TABLE K2
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 13-Week Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration ^a (mg/mL) | Determined Concentration ^b (mg/mL) | Difference from Target (%) |
|------------------|------------------------------|---|---|----------------------------------|
| F344/N Rats | | | | |
| 11 January 1990 | 11 January 1990 | 0.05 | 0.048 | ! 4 |
| | | 0.10 | 0.097 | ! 3 |
| | | 0.25 | 0.235 | ! 6 |
| | | 0.50 | 0.492 | ! 2 |
| | | 1.00 | 0.989 | ! 1 |
| | 26 January 1990 ^c | 0.05 | 0.044 | ! 12 |
| | | 0.10 | 0.096 | ! 4 |
| | | 0.25 | 0.246 | ! 2 |
| | | 0.50 | 0.487 | ! 3 |
| | | 1.00 | 0.973 | ! 3 |
| 1 March 1990 | 1 March 1990 | 0.05 | 0.051 | +2 |
| | | 0.10 | 0.100 | 0 |
| | | 0.25 | 0.249 | 0 |
| | | 0.50 | 0.501 | 0 |
| | | 1.00 | 0.973 | ! 3 |
| | 13 March 1990 ^c | 0.05 | 0.053 | +6 |
| | | 0.10 | 0.100 | 0 |
| | | 0.25 | 0.241 | ! 4 |
| | | 0.50 | 0.504 | +1 |
| | | 1.00 | 0.966 | ! 3 |
| 12 April 1990 | 16 April 1990 | 0.05 | 0.050 | 0 |
| | | 0.10 | 0.098 | ! 2 |
| | | 0.25 | 0.249 | 0 |
| | | 0.50 | 0.502 | 0 |
| | | 1.00 | 0.996 | 0 |
| | 25 April 1990 ^c | 0.05 | 0.050 | 0 |
| | | 0.10 | 0.097 | ! 3 |
| | | 0.25 | 0.249 | 0 |
| | | 0.50 | 0.506 | +1 |
| | | 1.00 | 0.993 | ! 1 |
| Wistar Rats | | | | |
| 15 February 1990 | 16 February 1990 | 0.05 | 0.050 | 0 |
| | | 0.10 | 0.100 | 0 |
| | | 0.25 | 0.254 | +2 |
| | | 0.50 | 0.507 | +1 |
| | | 1.00 | 1.005 | +1 |
| | 2 March 1990 ^c | 0.05 | 0.050 | 0 |
| | | 0.10 | 0.099 | ! 1 |
| | | 0.25 | 0.249 | 0 |
| | | 0.50 | 0.493 | ! 1 |
| | | 1.00 | 0.998 | 0 |

TABLE K2
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 13-Week Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|-------------------------|-------------------------------|------------------------------------|--|----------------------------------|
| Wistar Rats (continued) | | | | |
| 5 April 1990 | 5 April 1990 | 0.05 | 0.051 | +2 |
| | | 0.10 | 0.101 | +1 |
| | | 0.25 | 0.250 | 0 |
| | | 0.50 | 0.500 | 0 |
| | | 1.00 | 0.999 | 0 |
| | 16 April 1990 ^c | 0.05 | 0.049 | ! 2 |
| | | 0.10 | 0.097 | ! 3 |
| | | 0.25 | 0.248 | ! 1 |
| | | 0.50 | 0.494 | ! 1 |
| | | 1.00 | 0.996 | 0 |
| 17 May 1990 | 17 May 1990 | 0.05 | 0.048 | ! 4 |
| | | 0.10 | 0.099 | ! 1 |
| | | 0.25 | 0.248 | ! 1 |
| | | 0.50 | 0.494 | ! 1 |
| | | 1.00 | 1.006 | +1 |
| | 25 May 1990 ^c | 0.05 | 0.050 | 0 |
| | | 0.10 | 0.098 | ! 2 |
| | | 0.25 | 0.246 | ! 2 |
| | | 0.50 | 0.495 | ! 1 |
| | | 1.00 | 0.997 | 0 |
| Mice | | | | |
| 7 December 1989 | 7 December 1989 | 0.05 | 0.049 | ! 2 |
| | | 0.10 | 0.097 | ! 3 |
| | | 0.25 | 0.242 | ! 3 |
| | | 0.50 | 0.483 | ! 3 |
| | | 1.00 | 0.966 | ! 3 |
| | 27 December 1989 ^c | 0.05 | 0.051 | +2 |
| | | 0.10 | 0.099 | ! 1 |
| | | 0.25 | 0.246 | ! 2 |
| | | 0.50 | 0.504 | +1 |
| | | 1.00 | 0.986 | ! 1 |
| 25 January 1990 | 26 January 1990 | 0.05 | 0.052 | +4 |
| | | 0.10 | 0.097 | ! 3 |
| | | 0.25 | 0.246 | ! 2 |
| | | 0.50 | 0.487 | ! 3 |
| | | 1.00 | 0.981 | ! 2 |
| | 13 February 1990 ^c | 0.05 | 0.049 | ! 2 |
| | | 0.10 | 0.097 | ! 3 |
| | | 0.25 | 0.240 | ! 4 |
| | | 0.50 | 0.489 | ! 2 |
| | | 1.00 | 0.973 | ! 3 |

TABLE K2

Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 13-Week Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|-------------------------|----------------------------|------------------------------|----------------------------------|----------------------------|
| Mice (continued) | | | | |
| 1 March 1990 | 1 March 1990 | 0.05 | 0.051 | +2 |
| | | 0.10 | 0.100 | 0 |
| | | 0.25 | 0.249 | 0 |
| | | 0.50 | 0.501 | 0 |
| | | 1.00 | 0.973 | ! 3 |
| | 13 March 1990 ^c | 0.05 | 0.052 | +4 |
| | | 0.10 | 0.096 | ! 4 |
| | | 0.25 | 0.239 | ! 4 |
| | | 0.50 | 0.494 | ! 1 |
| | | 1.00 | 0.952 | ! 5 |

^a 0.05 mg/mL=50 ppm; 0.10 mg/mL=100 ppm; 0.25 mg/mL=250 ppm; 0.50 mg/mL=500 ppm; 1.00 mg/mL=1,000 ppm

^b Results of duplicate analyses

^c Animal room samples

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration ^a (mg/mL) | Determined Concentration ^b (mg/mL) | Difference from Target (%) | |
|------------------|--------------------------------|---|---|----------------------------------|-----|
| F344/N Rats | | | | | |
| 11 April 1991 | 12 April 1991 | 0.1 | 0.100 | 0 | |
| | | 0.2 | 0.196 | ! 2 | |
| | | 0.4 | 0.396 | ! 1 | |
| | 2 May 1991 ^c | 0.1 | 0.099 | ! 1 | |
| | | 0.2 | 0.199 | 0 | |
| | | 0.4 | 0.398 | 0 | |
| | 23 May 1991 | 24 May 1991 | 0.1 | 0.099 | ! 1 |
| | | | 0.1 | 0.099 | ! 1 |
| | | | 0.2 | 0.198 | ! 1 |
| 0.2 | | | 0.198 | ! 1 | |
| 0.4 | | | 0.394 | ! 1 | |
| 0.4 | | | 0.399 | 0 | |
| 1 July 1991 | 1-3 July 1991 | 0.1 | 0.100 | 0 | |
| | | 0.1 | 0.100 | 0 | |
| | | 0.2 | 0.202 | +1 | |
| | | 0.2 | 0.201 | +1 | |
| | | 0.4 | 0.388 | ! 3 | |
| | | 0.4 | 0.211 | ! 47 | |
| 3 July 1991 | 3 July 1991 | 0.4 | 0.398 ^d | 0 | |
| 29 August 1991 | 30 August 1991 | 0.1 | 0.101 | +1 | |
| | | 0.1 | 0.098 | ! 2 | |
| | | 0.2 | 0.197 | ! 1 | |
| | | 0.2 | 0.191 | ! 4 | |
| | | 0.4 | 0.374 | ! 6 | |
| | | 0.4 | 0.390 | ! 2 | |
| | 20 September 1991 ^c | 0.1 | 0.101 | +1 | |
| | | 0.1 | 0.098 | ! 2 | |
| | | 0.2 | 0.201 | +1 | |
| | | 0.2 | 0.201 | +1 | |
| | | 0.4 | 0.400 | 0 | |
| | | 0.4 | 0.396 | ! 1 | |
| 24 October 1991 | 25 October 1991 | 0.1 | 0.102 | +2 | |
| | | 0.2 | 0.209 | +5 | |
| | | 0.4 | 0.416 | +4 | |
| 19 December 1991 | 20 December 1991 | 0.1 | 0.099 | ! 1 | |
| | | 0.2 | 0.197 | ! 1 | |
| | | 0.4 | 0.398 | 0 | |

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|--------------------------------|-------------------------------|------------------------------------|--|----------------------------------|
| F344/N Rats (continued) | | | | |
| 13 February 1992 | 14 February 1992 | 0.1 | 0.100 | 0 |
| | | 0.2 | 0.198 | ! 1 |
| | | 0.4 | 0.392 | ! 2 |
| | 3 March 1992 ^c | 0.1 | 0.098 | ! 2 |
| | | 0.2 | 0.195 | ! 2 |
| | | 0.4 | 0.397 | ! 1 |
| 9 April 1992 | 10 April 1992 | 0.1 | 0.100 | 0 |
| | | 0.1 | 0.098 | ! 2 |
| | | 0.2 | 0.197 | ! 1 |
| | | 0.2 | 0.199 | 0 |
| | | 0.4 | 0.392 | ! 2 |
| | | 0.4 | 0.402 | +1 |
| 4 June 1992 | 5 June 1992 | 0.1 | 0.097 | ! 3 |
| | | 0.2 | 0.198 | ! 1 |
| | | 0.4 | 0.396 | ! 1 |
| 30 July 1992 | 31 July 1992 | 0.1 | 0.098 | ! 2 |
| | | 0.2 | 0.193 | ! 3 |
| | | 0.4 | 0.393 | ! 2 |
| | 2 September 1992 ^c | 0.1 | 0.097 | ! 3 |
| | | 0.2 | 0.195 | ! 2 |
| | | 0.4 | 0.383 | ! 4 |
| 24 September 1992 | 25 September 1992 | 0.1 | 0.102 | +2 |
| | | 0.2 | 0.201 | +1 |
| | | 0.4 | 0.399 | 0 |
| 19 November 1992 | 20-24 November 1992 | 0.1 | 0.101 | +1 |
| | | 0.2 | 0.206 | +3 |
| | | 0.4 | 0.395 | ! 1 |
| 14 January 1993 | 15 January 1993 | 0.1 | 0.098 | ! 2 |
| | | 0.1 | 0.099 | ! 1 |
| | | 0.2 | 0.193 | ! 3 |
| | | 0.2 | 0.198 | ! 1 |
| | | 0.4 | 0.395 | ! 1 |
| | | 0.4 | 0.392 | ! 2 |
| | 8 February 1993 ^c | 0.1 | 0.090 | ! 10 |
| | | 0.1 | 0.095 | ! 5 |
| | | 0.2 | 0.195 | ! 2 |
| | | 0.2 | 0.195 | ! 2 |
| | | 0.4 | 0.386 | ! 3 |
| | | 0.4 | 0.386 | ! 3 |
| 11 March 1993 | 12 March 1993 | 0.1 | 0.098 | ! 2 |
| | | 0.2 | 0.197 | ! 1 |
| | | 0.4 | 0.396 | ! 1 |

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|--------------------|------------------------------|------------------------------------|--|----------------------------------|
| Wistar Rats | | | | |
| 2 May 1991 | 2 May 1991 | 0.1 | 0.099 | ! 1 |
| | | 0.2 | 0.198 | ! 1 |
| | | 0.4 | 0.397 | ! 1 |
| | 24 May 1991 ^c | 0.1 | 0.099 | ! 1 |
| | | 0.2 | 0.197 | ! 1 |
| | | 0.4 | 0.398 | 0 |
| 1 July 1991 | 1-2 July 1991 | 0.1 | 0.100 | 0 |
| | | 0.2 | 0.190 | ! 5 |
| | | 0.4 | 0.396 | ! 1 |
| 29 August 1991 | 30 August 1991 | 0.1 | 0.099 | ! 1 |
| | | 0.2 | 0.197 | ! 1 |
| | | 0.4 | 0.408 | +2 |
| 24 October 1991 | 25 October 1991 | 0.1 | 0.104 | +4 |
| | | 0.1 | 0.101 | +1 |
| | | 0.2 | 0.210 | +5 |
| | | 0.2 | 0.206 | +3 |
| | | 0.4 | 0.408 | +2 |
| | | 0.4 | 0.416 | +4 |
| | 1 November 1991 ^c | 0.1 | 0.095 | ! 5 |
| | | 0.1 | 0.098 | ! 2 |
| | | 0.2 | 0.197 | ! 1 |
| | | 0.2 | 0.197 | ! 1 |
| | | 0.4 | 0.403 | +1 |
| | | 0.4 | 0.403 | +1 |
| 19 December 1991 | 20 December 1991 | 0.1 | 0.098 | ! 2 |
| | | 0.2 | 0.195 | ! 2 |
| | | 0.4 | 0.395 | ! 1 |
| 13 February 1992 | 14 February 1992 | 0.1 | 0.100 | 0 |
| | | 0.2 | 0.199 | 0 |
| | | 0.4 | 0.398 | 0 |
| 9 April 1992 | 10 April 1992 | 0.1 | 0.100 | 0 |
| | | 0.2 | 0.198 | ! 1 |
| | | 0.4 | 0.394 | ! 1 |
| | 27 April 1992 ^c | 0.1 | 0.099 | ! 1 |
| | | 0.2 | 0.198 | ! 1 |
| | | 0.4 | 0.421 | +5 |
| 4 June 1992 | 5 June 1992 | 0.1 | 0.099 | ! 1 |
| | | 0.2 | 0.198 | ! 1 |
| | | 0.4 | 0.390 | ! 2 |
| 30 July 1992 | 31 July 1992 | 0.1 | 0.099 | ! 1 |
| | | 0.2 | 0.195 | ! 2 |
| | | 0.4 | 0.390 | ! 2 |

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) | | |
|-------------------------|-----------------------------|------------------------------------|--|----------------------------------|-------|-----|
| Wistar Rats (continued) | | | | | | |
| 24 September 1992 | 25 September 1992 | 0.1 | 0.101 | +1 | | |
| | | 0.2 | 0.200 | 0 | | |
| | | 0.4 | 0.385 | ! 4 | | |
| | 9 October 1992 ^c | 0.1 | 0.100 | 0 | | |
| | | 0.2 | 0.198 | ! 1 | | |
| | | 0.4 | 0.398 | 0 | | |
| 19 November 1992 | 20-24 November 1992 | 0.1 | 0.101 | +1 | | |
| | | 0.1 | 0.099 | ! 1 | | |
| | | 0.1 | 0.099 | ! 1 | | |
| | | 0.2 | 0.202 | +1 | | |
| | | 0.2 | 0.198 | ! 1 | | |
| | | 0.2 | 0.199 | 0 | | |
| | | 0.4 | 0.401 | 0 | | |
| | | 0.4 | 0.399 | 0 | | |
| | | 0.4 | 0.394 | ! 1 | | |
| | | 14 January 1993 | 15 January 1993 | 0.1 | 0.100 | 0 |
| | | | | 0.2 | 0.193 | ! 3 |
| 0.4 | 0.389 | | | ! 3 | | |
| 11 March 1993 | 12 March 1993 | 0.1 | 0.100 | 0 | | |
| | | 0.2 | 0.197 | ! 1 | | |
| | | 0.4 | 0.394 | ! 1 | | |
| | 1 April 1993 ^c | 0.1 | 0.099 | ! 1 | | |
| | | 0.2 | 0.197 | ! 1 | | |
| | | 0.4 | 0.393 | ! 2 | | |
| 22 April 1993 | 23 April 1993 | 0.1 | 0.102 | +2 | | |
| | | 0.2 | 0.201 | +1 | | |
| | | 0.4 | 0.405 | +1 | | |
| Male Mice | | | | | | |
| 21 March 1991 | 22 March 1991 | 0.25 | 0.249 | 0 | | |
| | | 0.50 | 0.498 | 0 | | |
| | | 1.00 | 0.990 | ! 1 | | |
| | 12 April 1991 ^c | 0.25 | 0.246 | ! 2 | | |
| | | 0.50 | 0.492 | ! 2 | | |
| | | 1.00 | 0.979 | ! 2 | | |
| 9 May 1991 | 10 May 1991 | 0.25 | 0.244 | ! 2 | | |
| | | 0.50 | 0.494 | ! 1 | | |
| | | 1.00 | 0.981 | ! 2 | | |
| 1 July 1991 | 1 July 1991 | 0.25 | 0.246 | ! 2 | | |
| | | 0.50 | 0.491 | ! 2 | | |
| | | 1.00 | 0.986 | ! 1 | | |

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|------------------------------|--------------------------------|------------------------------------|--|----------------------------------|
| Male Mice (continued) | | | | |
| 29 August 1991 | 30 August 1991 | 0.25 | 0.236 | ! 6 |
| | | 0.50 | 0.479 | ! 4 |
| | | 1.00 | 0.944 | ! 6 |
| | 20 September 1991 ^c | 0.25 | 0.251 | 0 |
| | | 0.50 | 0.513 | +3 |
| | | 1.00 | 1.000 | 0 |
| 24 October 1991 | 25 October 1991 | 0.25 | 0.258 | +3 |
| | | 0.50 | 0.520 | +4 |
| | | 1.00 | 1.025 | +3 |
| 19 December 1991 | 20 December 1991 | 0.25 | 0.255 | +2 |
| | | 0.50 | 0.500 | 0 |
| | | 1.00 | 0.991 | ! 1 |
| 13 February 1992 | 14 February 1992 | 0.25 | 0.246 | ! 2 |
| | | 0.50 | 0.489 | ! 2 |
| | | 1.00 | 0.990 | ! 1 |
| | 3 March 1992 ^c | 0.25 | 0.244 | ! 2 |
| | | 0.50 | 0.488 | ! 2 |
| | | 1.00 | 0.977 | ! 2 |
| 9 April 1992 | 10 April 1992 | 0.25 | 0.245 | ! 2 |
| | | 0.50 | 0.484 | ! 3 |
| | | 1.00 | 0.981 | ! 2 |
| 4 June 1992 | 5 June 1992 | 0.25 | 0.246 | ! 2 |
| | | 0.50 | 0.487 | ! 3 |
| | | 1.00 | 0.970 | ! 3 |
| 30 July 1992 | 31 July 1992 | 0.25 | 0.245 | ! 2 |
| | | 0.50 | 0.492 | ! 2 |
| | | 1.00 | 0.973 | ! 3 |
| | 2 September 1992 ^c | 0.25 | 0.244 | ! 2 |
| | | 0.50 | 0.501 | 0 |
| | | 1.00 | 0.988 | ! 1 |
| 24 September 1992 | 25 September 1992 | 0.25 | 0.253 | +1 |
| | | 0.50 | 0.495 | ! 1 |
| | | 1.00 | 0.999 | 0 |
| 19 November 1992 | 20-24 November 1992 | 0.25 | 0.247 | ! 1 |
| | | 0.50 | 0.496 | ! 1 |
| | | 1.00 | 0.987 | ! 1 |

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) | |
|-----------------------|--------------------------------|------------------------------------|--|----------------------------------|-----|
| Male Mice (continued) | | | | | |
| 14 January 1993 | 15 January 1993 | 0.25 | 0.250 | 0 | |
| | | 0.50 | 0.487 | ! 3 | |
| | | 1.00 | 0.972 | ! 3 | |
| | 8 February 1993 ^c | 0.25 | 0.245 | ! 2 | |
| | | 0.50 | 0.476 | ! 5 | |
| | | 1.00 | 0.961 | ! 4 | |
| | 11 March 1993 | 12 March 1993 | 0.25 | 0.252 | +1 |
| | | | 0.50 | 0.497 | ! 1 |
| | | | 1.00 | 0.981 | ! 2 |
| Female Mice | | | | | |
| 21 March 1991 | 22 March 1991 | 0.125 | 0.124 | ! 1 | |
| | | 0.250 | 0.248 | ! 1 | |
| | | 0.500 | 0.504 | +1 | |
| | 12 April 1991 ^c | 0.125 | 0.126 | +1 | |
| | | 0.250 | 0.244 | ! 2 | |
| | | 0.500 | 0.495 | ! 1 | |
| | 9 May 1991 | 10 May 1991 | 0.125 | 0.122 | ! 2 |
| | | | 0.250 | 0.246 | ! 2 |
| | | | 0.500 | 0.490 | ! 2 |
| 1 July 1991 | 1 July 1991 | 0.125 | 0.124 | ! 1 | |
| | | 0.250 | 0.251 | 0 | |
| | | 0.500 | 0.494 | ! 1 | |
| 29 August 1991 | 30 August 1991 | 0.125 | 0.118 | ! 6 | |
| | | 0.250 | 0.234 | ! 6 | |
| | | 0.500 | 0.473 | ! 5 | |
| | 20 September 1991 ^c | 0.125 | 0.125 | 0 | |
| | | 0.250 | 0.245 | ! 2 | |
| | | 0.500 | 0.499 | 0 | |
| | 24 October 1991 | 25 October 1991 | 0.125 | 0.126 | +1 |
| | | | 0.250 | 0.260 | +4 |
| | | | 0.500 | 0.517 | +3 |
| 19 December 1991 | 20 December 1991 | 0.125 | 0.127 | +2 | |
| | | 0.250 | 0.248 | ! 1 | |
| | | 0.500 | 0.495 | ! 1 | |

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|--------------------------------|-------------------------------|------------------------------------|--|----------------------------------|
| Female Mice (continued) | | | | |
| 13 February 1992 | 14 February 1992 | 0.125 | 0.125 | 0 |
| | | 0.250 | 0.247 | ! 1 |
| | | 0.500 | 0.491 | ! 2 |
| | 3 March 1992 ^c | 0.125 | 0.124 | ! 1 |
| | | 0.250 | 0.248 | ! 1 |
| | | 0.500 | 0.490 | ! 2 |
| 9 April 1992 | 10 April 1992 | 0.125 | 0.123 | ! 2 |
| | | 0.250 | 0.245 | ! 2 |
| | | 0.500 | 0.491 | ! 2 |
| 4 June 1992 | 5 June 1992 | 0.125 | 0.120 | ! 4 |
| | | 0.250 | 0.243 | ! 3 |
| | | 0.500 | 0.488 | ! 2 |
| 30 July 1992 | 31 July 1992 | 0.125 | 0.127 | +2 |
| | | 0.250 | 0.244 | ! 2 |
| | | 0.500 | 0.491 | ! 2 |
| | 2 September 1992 ^c | 0.125 | 0.126 | +1 |
| | | 0.250 | 0.249 | 0 |
| | | 0.500 | 0.502 | 0 |
| 24 September 1992 | 25 September 1992 | 0.125 | 0.127 | +2 |
| | | 0.250 | 0.253 | +1 |
| | | 0.500 | 0.494 | ! 1 |
| 19 November 1992 | 20-24 November 1992 | 0.125 | 0.125 | 0 |
| | | 0.250 | 0.249 | 0 |
| | | 0.500 | 0.482 | ! 4 |
| 14 January 1993 | 15 January 1993 | 0.125 | 0.122 | ! 2 |
| | | 0.250 | 0.245 | ! 2 |
| | | 0.500 | 0.483 | ! 3 |
| | 8 February 1993 ^c | 0.125 | 0.118 | ! 6 |
| | | 0.250 | 0.245 | ! 2 |
| | | 0.500 | 0.483 | ! 3 |
| 11 March 1993 | 12 March 1993 | 0.125 | 0.127 | +2 |
| | | 0.250 | 0.247 | ! 1 |
| | | 0.500 | 0.498 | 0 |

^a 0.1 mg/mL=100 ppm; 0.125 mg/mL=125 ppm; 0.2 mg/mL=200 ppm; 0.25 mg/mL=250 ppm; 0.4 mg/mL=400 ppm; 0.50 mg/mL=500 ppm;

1.00 mg/mL=1,000 ppm

^b Results of duplicate analyses

^c Animal room samples

^d Results of remix

TABLE K4
Results of Referee Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats,
and Mice in the 13-Week Drinking Water Studies of Pyridine

| Date Prepared | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | |
|--------------------|---------------------------------|----------------------------------|---------------------------------|
| | | Study Laboratory ^a | Referee Laboratory ^b |
| | | | |
| F344/N Rats | | | |
| 11 January 1990 | 0.50 | 0.492 | 0.512 ± 0.005 |
| | | | |
| Wistar Rats | | | |
| 15 February 1990 | 1.00 | 1.005 | 0.994 ± 0.002 |
| | | | |
| Mice | | | |
| 7 December 1989 | 0.10 | 0.097 | 0.106 ± 0.000 |

^a Results of duplicate analyses

^b Results of triplicate analyses (mean ± standard error)

APPENDIX L

WATER AND COMPOUND CONSUMPTION IN THE 2-YEAR DRINKING WATER STUDIES OF PYRIDINE

| | | |
|-----------------|--|------------|
| TABLE L1 | Water and Compound Consumption by Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine | 314 |
| TABLE L2 | Water and Compound Consumption by Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine | 315 |
| TABLE L3 | Water and Compound Consumption by Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine | 316 |
| TABLE L4 | Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of Pyridine | 317 |
| TABLE L5 | Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of Pyridine | 318 |

TABLE L1
Water and Compound Consumption by Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| Week | 0 ppm | | 100 ppm | | | 200 ppm | | | 400 ppm | | |
|-----------------------|-------------------------------|-----------------------|------------------|-----------------------|--------------------------------------|------------------|-----------------------|-------------------------|------------------|-----------------------|-------------------------|
| | Water (g/day) ^a | Body Weight (g) | Water (g/day) | Body Weight (g) | Dose/ Day ^b (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) |
| 1 | 20.4 | 136 | 19.5 | 135 | 14 | 18.6 | 135 | 28 | 18.5 | 136 | 55 |
| 2 | 21.4 | 173 | 20.7 | 172 | 12 | 20.9 | 169 | 25 | 21.5 | 167 | 51 |
| 3 | 22.6 | 207 | 22.1 | 208 | 11 | 21.8 | 206 | 21 | 24.3 | 201 | 48 |
| 4 | 20.5 | 236 | 21.2 | 234 | 9 | 19.9 | 232 | 17 | 24.1 | 227 | 43 |
| 5 | 22.1 | 255 | 21.6 | 253 | 9 | 23.0 | 250 | 18 | 23.4 | 245 | 38 |
| 6 | 20.6 | 275 | 21.1 | 267 | 8 | 21.7 | 272 | 16 | 22.6 | 258 | 35 |
| 7 | 20.4 | 293 | 20.7 | 286 | 7 | 21.5 | 289 | 15 | 22.8 | 272 | 34 |
| 8 | 22.4 | 302 | 22.8 | 295 | 8 | 22.6 | 295 | 15 | 24.9 | 282 | 35 |
| 9 | 22.4 | 314 | 22.4 | 309 | 7 | 22.5 | 306 | 15 | 24.7 | 291 | 34 |
| 10 | 23.3 | 331 | 22.9 | 326 | 7 | 21.8 | 323 | 14 | 25.8 | 309 | 33 |
| 11 | 22.3 | 333 | 21.4 | 329 | 7 | 22.0 | 328 | 13 | 26.9 | 311 | 35 |
| 12 | 24.9 | 342 | 23.6 | 339 | 7 | 22.7 | 340 | 13 | 26.9 | 323 | 33 |
| 13 | 21.5 | 351 | 20.6 | 349 | 6 | 21.6 | 348 | 12 | 24.6 | 328 | 30 |
| 17 | 21.8 | 384 | 21.4 | 382 | 6 | 20.3 | 378 | 11 | 23.8 | 355 | 27 |
| 21 | 22.5 | 409 | 21.3 | 405 | 5 | 22.1 | 404 | 11 | 23.6 | 376 | 25 |
| 25 | 22.4 | 426 | 22.2 | 420 | 5 | 22.7 | 420 | 11 | 25.7 | 392 | 26 |
| 29 | 22.7 | 437 | 23.0 | 431 | 5 | 22.7 | 433 | 11 | 25.7 | 403 | 26 |
| 33 | 22.9 | 453 | 23.3 | 448 | 5 | 23.5 | 448 | 11 | 24.8 | 421 | 24 |
| 37 | 24.5 | 465 | 21.8 | 461 | 5 | 22.3 | 460 | 10 | 25.0 | 434 | 23 |
| 41 | 25.3 | 478 | 22.8 | 468 | 5 | 25.0 | 469 | 11 | 25.7 | 443 | 23 |
| 45 | 21.6 | 483 | 20.8 | 480 | 4 | 20.8 | 480 | 9 | 23.1 | 452 | 20 |
| 49 | 22.4 | 489 | 20.9 | 479 | 4 | 22.3 | 480 | 9 | 24.1 | 453 | 21 |
| 53 | 21.7 | 487 | 21.6 | 482 | 5 | 22.3 | 482 | 9 | 25.8 | 453 | 23 |
| 57 | 23.8 | 502 | 23.0 | 489 | 5 | 26.1 | 484 | 11 | 29.3 | 462 | 25 |
| 61 | 24.1 | 503 | 22.7 | 491 | 5 | 25.4 | 487 | 10 | 28.7 | 459 | 25 |
| 65 | 26.0 | 508 | 25.4 | 492 | 5 | 28.8 | 484 | 12 | 32.3 | 455 | 28 |
| 69 | 25.0 | 511 | 24.3 | 500 | 5 | 29.0 | 485 | 12 | 35.2 | 457 | 31 |
| 73 | 25.6 | 511 | 25.7 | 500 | 5 | 30.0 | 480 | 13 | 37.4 | 446 | 34 |
| 77 | 24.5 | 510 | 24.1 | 497 | 5 | 27.9 | 475 | 12 | 35.8 | 446 | 32 |
| 81 | 26.1 | 494 | 26.5 | 497 | 5 | 30.1 | 467 | 13 | 40.3 | 441 | 37 |
| 85 | 27.7 | 501 | 28.3 | 486 | 6 | 35.5 | 462 | 15 | 45.1 | 428 | 42 |
| 89 | 29.3 | 499 | 29.8 | 484 | 6 | 34.7 | 440 | 16 | 43.7 | 414 | 42 |
| 93 | 32.5 | 501 | 31.7 | 478 | 7 | 38.0 | 428 | 18 | 46.7 | 406 | 46 |
| 97 | 30.6 | 491 | 29.2 | 464 | 6 | 35.0 | 414 | 17 | 40.3 | 391 | 41 |
| 101 | 36.3 | 468 | 36.6 | 458 | 8 | 37.0 | 397 | 19 | 49.0 | 388 | 51 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 21.9 | 273 | 21.6 | 270 | 9 | 21.6 | 269 | 17 | 23.9 | 258 | 39 |
| 14-52 | 22.9 | 447 | 21.9 | 441 | 5 | 22.4 | 441 | 10 | 24.6 | 414 | 24 |
| 53-101 | 27.2 | 499 | 26.8 | 486 | 6 | 30.8 | 460 | 14 | 37.6 | 434 | 35 |

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

TABLE L2
Water and Compound Consumption by Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

| Week | 0 ppm | | 100 ppm | | | 200 ppm | | | 400 ppm | | |
|-----------------------|-------------------------------|-----------------------|------------------|-----------------------|--------------------------------------|------------------|-----------------------|-------------------------|------------------|-----------------------|-------------------------|
| | Water (g/day) ^a | Body Weight (g) | Water (g/day) | Body Weight (g) | Dose/ Day ^b (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) |
| 1 | 16.2 | 110 | 16.9 | 110 | 15 | 16.7 | 110 | 30 | 17.4 | 111 | 63 |
| 2 | 16.4 | 129 | 16.7 | 128 | 13 | 17.1 | 127 | 27 | 18.7 | 124 | 60 |
| 3 | 16.4 | 144 | 16.9 | 145 | 12 | 18.0 | 143 | 25 | 17.7 | 139 | 51 |
| 4 | 15.2 | 152 | 16.1 | 152 | 11 | 16.8 | 151 | 22 | 16.9 | 148 | 46 |
| 5 | 17.2 | 160 | 15.2 | 160 | 10 | 15.1 | 159 | 19 | 17.1 | 155 | 44 |
| 6 | 16.7 | 167 | 14.5 | 167 | 9 | 14.5 | 164 | 18 | 16.5 | 160 | 41 |
| 7 | 15.3 | 173 | 15.5 | 173 | 9 | 15.3 | 171 | 18 | 16.6 | 167 | 40 |
| 8 | 16.2 | 180 | 16.7 | 179 | 9 | 16.0 | 176 | 18 | 17.2 | 170 | 41 |
| 9 | 16.3 | 183 | 17.5 | 183 | 10 | 17.0 | 178 | 19 | 18.8 | 173 | 43 |
| 10 | 16.2 | 186 | 16.9 | 185 | 9 | 17.0 | 181 | 19 | 18.5 | 175 | 42 |
| 11 | 16.0 | 192 | 16.5 | 190 | 9 | 17.6 | 185 | 19 | 17.1 | 178 | 38 |
| 12 | 15.3 | 196 | 15.9 | 194 | 8 | 16.1 | 187 | 17 | 16.2 | 182 | 36 |
| 13 | 14.3 | 198 | 14.7 | 197 | 8 | 15.0 | 191 | 16 | 15.7 | 185 | 34 |
| 17 | 14.3 | 213 | 16.1 | 210 | 8 | 17.0 | 204 | 17 | 17.3 | 196 | 35 |
| 21 | 14.8 | 223 | 15.4 | 220 | 7 | 16.6 | 212 | 16 | 17.4 | 205 | 34 |
| 25 | 15.9 | 228 | 16.1 | 225 | 7 | 16.3 | 218 | 15 | 18.2 | 208 | 35 |
| 29 | 15.1 | 234 | 16.3 | 233 | 7 | 17.3 | 224 | 15 | 18.7 | 214 | 35 |
| 33 | 17.0 | 242 | 17.2 | 238 | 7 | 17.7 | 228 | 16 | 19.3 | 220 | 35 |
| 37 | 14.9 | 251 | 15.6 | 247 | 6 | 16.4 | 239 | 14 | 16.8 | 225 | 30 |
| 41 | 16.9 | 261 | 17.2 | 257 | 7 | 17.7 | 247 | 14 | 20.0 | 234 | 34 |
| 45 | 14.6 | 270 | 15.6 | 269 | 6 | 16.7 | 257 | 13 | 17.6 | 240 | 29 |
| 49 | 15.5 | 279 | 16.2 | 280 | 6 | 15.3 | 266 | 12 | 17.9 | 247 | 29 |
| 53 | 15.8 | 285 | 16.4 | 287 | 6 | 17.3 | 273 | 13 | 18.6 | 252 | 30 |
| 57 | 17.2 | 288 | 18.1 | 290 | 6 | 17.7 | 273 | 13 | 21.0 | 255 | 33 |
| 61 | 16.5 | 299 | 17.1 | 297 | 6 | 18.7 | 280 | 13 | 20.7 | 258 | 32 |
| 65 | 18.7 | 301 | 19.1 | 302 | 6 | 18.8 | 284 | 13 | 22.6 | 259 | 35 |
| 69 | 18.7 | 310 | 18.7 | 308 | 6 | 20.4 | 289 | 14 | 23.1 | 269 | 34 |
| 73 | 19.0 | 314 | 18.8 | 313 | 6 | 20.9 | 292 | 14 | 24.2 | 275 | 35 |
| 77 | 19.3 | 322 | 19.7 | 313 | 6 | 19.6 | 299 | 13 | 23.3 | 282 | 33 |
| 81 | 19.5 | 326 | 21.3 | 323 | 7 | 21.6 | 299 | 15 | 23.6 | 283 | 33 |
| 85 | 21.0 | 330 | 23.0 | 327 | 7 | 24.0 | 306 | 16 | 26.5 | 281 | 38 |
| 89 | 18.0 | 331 | 20.0 | 328 | 6 | 19.9 | 306 | 13 | 22.5 | 286 | 32 |
| 93 | 21.2 | 338 | 24.6 | 332 | 7 | 24.3 | 307 | 16 | 27.7 | 286 | 39 |
| 95 | 19.5 | 334 | 20.8 | 335 | 6 | 21.4 | 305 | 14 | 23.9 | 281 | 34 |
| 97 | 20.3 | 344 | 21.9 | 332 | 7 | 24.0 | 306 | 16 | 23.9 | 286 | 34 |
| 99 | 19.6 | 340 | 20.7 | 333 | 6 | 21.5 | 301 | 14 | 21.2 | 286 | 30 |
| 101 | 18.9 | 337 | 21.6 | 333 | 7 | 24.0 | 298 | 16 | 23.3 | 284 | 33 |
| 104 | 20.6 | 342 | 21.2 | 327 | 7 | 24.4 | 303 | 16 | 26.2 | 289 | 36 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 16.0 | 167 | 16.2 | 166 | 10 | 16.3 | 163 | 21 | 17.3 | 159 | 45 |
| 14-52 | 15.4 | 245 | 16.2 | 242 | 7 | 16.8 | 233 | 15 | 18.1 | 221 | 33 |
| 53-104 | 19.0 | 321 | 20.2 | 318 | 6 | 21.2 | 295 | 14 | 23.3 | 276 | 34 |

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

TABLE L3
Water and Compound Consumption by Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

| Week | 0 ppm | | 100 ppm | | | 200 ppm | | | 400 ppm | | |
|-----------------------|-------------------------------|-----------------------|------------------|-----------------------|--------------------------------------|------------------|-----------------------|-------------------------|------------------|-----------------------|-------------------------|
| | Water (g/day) ^a | Body Weight (g) | Water (g/day) | Body Weight (g) | Dose/ Day ^b (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) |
| 1 | 37.6 | 201 | 37.5 | 198 | 19 | 39.3 | 199 | 40 | 35.9 | 198 | 72 |
| 2 | 40.9 | 255 | 38.9 | 250 | 16 | 39.8 | 246 | 32 | 37.9 | 240 | 63 |
| 3 | 38.9 | 294 | 40.2 | 289 | 14 | 41.3 | 285 | 29 | 41.9 | 280 | 60 |
| 4 | 42.1 | 327 | 42.1 | 326 | 13 | 43.9 | 321 | 27 | 42.7 | 312 | 55 |
| 5 | 46.3 | 357 | 48.6 | 359 | 14 | 48.5 | 347 | 28 | 45.7 | 345 | 53 |
| 6 | 39.4 | 382 | 39.3 | 380 | 10 | 39.9 | 372 | 21 | 38.9 | 358 | 43 |
| 7 | 40.8 | 413 | 44.3 | 411 | 11 | 44.4 | 402 | 22 | 46.0 | 388 | 47 |
| 8 | 47.4 | 426 | 43.5 | 428 | 10 | 47.1 | 412 | 23 | 45.6 | 400 | 46 |
| 9 | 53.3 | 448 | 49.2 | 446 | 11 | 49.5 | 435 | 23 | 48.7 | 419 | 47 |
| 10 | 42.7 | 464 | 41.4 | 463 | 9 | 43.3 | 452 | 19 | 43.2 | 431 | 40 |
| 11 | 50.3 | 479 | 46.3 | 478 | 10 | 47.0 | 463 | 20 | 47.0 | 443 | 42 |
| 12 | 48.2 | 494 | 47.3 | 492 | 10 | 47.3 | 479 | 20 | 43.9 | 457 | 38 |
| 13 | 46.8 | 506 | 46.7 | 503 | 9 | 46.6 | 490 | 19 | 46.3 | 466 | 40 |
| 17 | 44.0 | 546 | 42.3 | 542 | 8 | 41.9 | 527 | 16 | 41.0 | 502 | 33 |
| 21 | 46.5 | 569 | 42.8 | 575 | 7 | 41.5 | 562 | 15 | 44.8 | 528 | 34 |
| 25 | 41.9 | 599 | 39.4 | 602 | 7 | 41.0 | 583 | 14 | 42.9 | 552 | 31 |
| 29 | 40.4 | 627 | 36.7 | 630 | 6 | 40.0 | 612 | 13 | 41.6 | 576 | 29 |
| 33 | 43.6 | 658 | 42.8 | 657 | 7 | 39.9 | 638 | 13 | 44.2 | 599 | 30 |
| 37 | 46.8 | 672 | 46.6 | 673 | 7 | 48.1 | 651 | 15 | 48.6 | 610 | 32 |
| 41 | 38.4 | 691 | 38.8 | 686 | 6 | 39.2 | 664 | 12 | 40.3 | 627 | 26 |
| 45 | 43.5 | 715 | 42.9 | 711 | 6 | 43.0 | 684 | 13 | 44.0 | 642 | 27 |
| 49 | 40.5 | 736 | 40.5 | 719 | 6 | 41.9 | 695 | 12 | 44.5 | 654 | 27 |
| 53 | 50.9 | 755 | 48.3 | 735 | 7 | 52.6 | 705 | 15 | 53.5 | 662 | 32 |
| 57 | 45.4 | 774 | 47.3 | 748 | 6 | 48.8 | 714 | 14 | 50.7 | 668 | 30 |
| 61 | 54.7 | 789 | 53.9 | 753 | 7 | 59.4 | 718 | 17 | 57.4 | 669 | 34 |
| 65 | 49.8 | 795 | 52.5 | 757 | 7 | 55.6 | 720 | 15 | 55.7 | 661 | 34 |
| 69 | 54.3 | 800 | 55.5 | 739 | 8 | 56.7 | 699 | 16 | 58.2 | 658 | 35 |
| 73 | 54.6 | 803 | 60.1 | 736 | 8 | 59.8 | 706 | 17 | 62.6 | 657 | 38 |
| 77 | 56.3 | 797 | 60.5 | 725 | 8 | 63.2 | 717 | 18 | 63.7 | 644 | 40 |
| 81 | 58.1 | 799 | 66.8 | 698 | 10 | 64.3 | 698 | 18 | 62.2 | 624 | 40 |
| 85 | 60.1 | 782 | 65.1 | 707 | 9 | 64.4 | 699 | 18 | 57.4 | 630 | 36 |
| 89 | 60.5 | 775 | 68.4 | 692 | 10 | 67.0 | 676 | 20 | 64.6 | 614 | 42 |
| 93 | 69.3 | 779 | 69.2 | 678 | 10 | 67.7 | 657 | 21 | 57.7 | 612 | 38 |
| 97 | 66.1 | 757 | 71.2 | 675 | 11 | 61.2 | 618 | 20 | 55.7 | 590 | 38 |
| 101 | 59.6 | 725 | 59.0 | 675 | 9 | 54.5 | 578 | 19 | 57.5 | 604 | 38 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 44.2 | 388 | 43.5 | 386 | 12 | 44.5 | 377 | 25 | 43.4 | 364 | 50 |
| 14-52 | 42.8 | 646 | 41.4 | 644 | 6 | 41.8 | 624 | 14 | 43.5 | 588 | 30 |
| 53-101 | 56.9 | 779 | 59.8 | 717 | 8 | 59.6 | 685 | 17 | 58.2 | 638 | 37 |

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

TABLE L4
Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of Pyridine

| Week | 0 ppm | | 250 ppm | | | 500 ppm | | | 1,000 ppm | | |
|-----------------------|-------------------------------|-----------------------|------------------|-----------------------|--------------------------------------|------------------|-----------------------|-------------------------|------------------|-----------------------|-------------------------|
| | Water (g/day) ^a | Body Weight (g) | Water (g/day) | Body Weight (g) | Dose/ Day ^b (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) |
| 1 | 6.5 | 26.1 | 6.8 | 25.9 | 66 | 5.7 | 25.8 | 109 | 5.6 | 25.8 | 218 |
| 2 | 5.7 | 27.6 | 5.6 | 27.4 | 51 | 5.2 | 27.3 | 95 | 4.5 | 26.6 | 171 |
| 3 | 5.6 | 29.2 | 5.3 | 28.7 | 46 | 5.2 | 29.0 | 90 | 4.3 | 28.4 | 150 |
| 4 | 5.7 | 30.9 | 5.3 | 30.5 | 44 | 5.0 | 30.7 | 82 | 4.3 | 30.1 | 142 |
| 5 | 5.6 | 32.8 | 5.3 | 32.3 | 41 | 5.5 | 32.2 | 85 | 4.9 | 30.6 | 160 |
| 6 | 5.3 | 33.9 | 5.0 | 34.2 | 36 | 4.6 | 33.5 | 69 | 3.9 | 32.0 | 123 |
| 7 | 5.5 | 35.4 | 5.0 | 35.4 | 35 | 4.9 | 35.3 | 69 | 3.8 | 33.9 | 112 |
| 8 | 5.0 | 37.6 | 4.9 | 37.1 | 33 | 4.6 | 36.7 | 63 | 3.9 | 35.6 | 110 |
| 9 | 5.4 | 38.7 | 5.2 | 37.9 | 34 | 5.0 | 37.7 | 66 | 4.3 | 36.5 | 119 |
| 10 | 5.4 | 39.6 | 5.7 | 40.1 | 36 | 5.2 | 39.8 | 65 | 4.4 | 37.7 | 117 |
| 11 | 5.7 | 40.6 | 6.4 | 41.0 | 39 | 5.3 | 41.0 | 64 | 4.5 | 38.8 | 117 |
| 12 | 5.5 | 41.8 | 5.8 | 42.3 | 34 | 5.0 | 41.7 | 60 | 5.0 | 39.8 | 126 |
| 13 | 5.5 | 42.4 | 5.9 | 42.9 | 34 | 5.6 | 42.7 | 66 | 5.2 | 40.6 | 129 |
| 17 | 5.2 | 47.0 | 5.3 | 46.2 | 28 | 5.2 | 45.9 | 57 | 4.3 | 43.5 | 99 |
| 21 | 6.9 | 48.1 | 6.5 | 48.3 | 34 | 5.8 | 47.4 | 61 | 4.1 | 45.2 | 90 |
| 25 | 5.3 | 50.0 | 5.4 | 49.6 | 27 | 5.1 | 49.9 | 51 | 4.7 | 47.5 | 98 |
| 29 | 7.0 | 49.6 | 6.6 | 50.8 | 32 | 7.1 | 51.3 | 69 | 5.6 | 48.5 | 116 |
| 33 | 5.2 | 51.6 | 5.1 | 51.7 | 25 | 4.9 | 51.1 | 48 | 4.5 | 50.0 | 91 |
| 37 | 5.4 | 53.2 | 5.2 | 52.9 | 24 | 4.7 | 53.0 | 45 | 4.3 | 51.8 | 84 |
| 41 | 6.8 | 54.5 | 6.9 | 53.8 | 32 | 6.4 | 53.7 | 60 | 6.6 | 52.5 | 126 |
| 45 | 5.8 | 54.1 | 6.4 | 53.9 | 30 | 6.0 | 54.4 | 55 | 5.0 | 52.7 | 95 |
| 49 | 6.6 | 55.3 | 6.0 | 54.6 | 28 | 7.2 | 55.4 | 65 | 4.9 | 53.4 | 92 |
| 53 | 6.1 | 55.4 | 5.8 | 55.6 | 26 | 5.7 | 56.2 | 51 | | | |
| 57 | 6.5 | 55.2 | 6.6 | 55.4 | 30 | 6.3 | 56.0 | 56 | 5.7 | 54.0 | 106 |
| 61 | 5.9 | 55.2 | 6.0 | 56.1 | 27 | 5.7 | 56.4 | 51 | 4.7 | 54.2 | 88 |
| 65 | 5.6 | 54.4 | 6.0 | 56.3 | 27 | 5.6 | 56.1 | 50 | 4.3 | 54.1 | 80 |
| 69 | 5.8 | 55.1 | 6.8 | 56.5 | 30 | 6.7 | 55.5 | 61 | 5.2 | 54.4 | 96 |
| 73 | 5.8 | 54.4 | 6.5 | 56.6 | 29 | 6.6 | 53.9 | 61 | 4.7 | 54.1 | 87 |
| 77 | 5.8 | 52.8 | 7.2 | 55.1 | 32 | 7.0 | 52.2 | 67 | 5.2 | 52.4 | 99 |
| 81 | 5.8 | 51.4 | 7.7 | 53.7 | 36 | 7.4 | 50.2 | 74 | 5.1 | 49.2 | 105 |
| 85 | 6.0 | 49.2 | 7.4 | 51.5 | 36 | 7.2 | 47.8 | 75 | 5.2 | 47.3 | 109 |
| 89 | 5.5 | 46.6 | 8.4 | 49.7 | 42 | 7.0 | 45.8 | 76 | 5.4 | 45.6 | 119 |
| 93 | 5.4 | 45.5 | 8.2 | 46.4 | 44 | 7.3 | 44.7 | 81 | 5.4 | 43.7 | 122 |
| 97 | 6.6 | 43.8 | 8.0 | 43.6 | 46 | 7.7 | 42.9 | 89 | 6.0 | 41.8 | 144 |
| 99 | 6.2 | 44.5 | 8.4 | 43.5 | 48 | 7.7 | 42.7 | 91 | 6.0 | 41.2 | 146 |
| 101 | 6.3 | 44.2 | 7.7 | 41.9 | 46 | 8.0 | 41.6 | 96 | 6.1 | 40.6 | 150 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 5.6 | 35.1 | 5.6 | 35.1 | 41 | 5.1 | 34.9 | 75 | 4.5 | 33.6 | 138 |
| 14-52 | 6.0 | 51.5 | 5.9 | 51.3 | 29 | 5.8 | 51.3 | 57 | 4.9 | 49.5 | 99 |
| 53-101 | 6.0 | 50.6 | 7.2 | 51.6 | 36 | 6.9 | 50.1 | 70 | 5.3 | 48.7 | 112 |

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

TABLE L5
Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of Pyridine

| Week | 0 ppm | | 125 ppm | | | 250 ppm | | | 500 ppm | | |
|-----------------------|-------------------------------|-----------------------|------------------|-----------------------|--------------------------------------|------------------|-----------------------|-------------------------|------------------|-----------------------|-------------------------|
| | Water (g/day) ^a | Body Weight (g) | Water (g/day) | Body Weight (g) | Dose/ Day ^b (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) | Water (g/day) | Body Weight (g) | Dose/ Day (mg/kg) |
| 1 | 7.3 | 20.8 | 7.5 | 20.7 | 45 | 6.8 | 20.6 | 82 | 6.3 | 20.5 | 154 |
| 2 | 6.9 | 21.8 | 6.6 | 21.4 | 39 | 6.6 | 21.6 | 76 | 5.7 | 21.5 | 132 |
| 3 | 7.5 | 23.2 | 7.1 | 22.8 | 39 | 7.4 | 22.8 | 81 | 6.5 | 22.6 | 144 |
| 4 | 6.5 | 24.1 | 6.8 | 24.0 | 35 | 6.4 | 23.9 | 67 | 5.6 | 23.7 | 118 |
| 5 | 7.7 | 25.5 | 7.0 | 25.3 | 34 | 6.9 | 25.5 | 68 | 5.4 | 25.6 | 106 |
| 6 | 6.1 | 26.7 | 5.8 | 26.5 | 28 | 6.3 | 26.3 | 59 | 4.9 | 26.9 | 90 |
| 7 | 5.8 | 28.2 | 5.8 | 28.4 | 25 | 6.1 | 28.8 | 53 | 5.1 | 28.5 | 89 |
| 8 | 6.0 | 29.6 | 5.4 | 29.9 | 23 | 5.6 | 29.8 | 47 | 5.0 | 30.0 | 84 |
| 9 | 5.9 | 31.1 | 5.7 | 30.1 | 24 | 5.7 | 30.8 | 46 | 5.2 | 30.4 | 85 |
| 10 | 5.5 | 31.7 | 6.3 | 32.0 | 24 | 6.4 | 32.7 | 49 | 5.7 | 32.9 | 86 |
| 11 | 6.7 | 33.3 | 6.3 | 33.2 | 24 | 6.2 | 33.7 | 46 | 5.7 | 33.7 | 85 |
| 12 | 7.1 | 34.1 | 6.4 | 34.2 | 23 | 6.0 | 35.2 | 43 | 5.4 | 35.1 | 76 |
| 13 | 6.1 | 35.8 | 5.7 | 35.5 | 20 | 5.4 | 36.5 | 37 | 5.4 | 36.3 | 74 |
| 17 | 5.0 | 40.2 | 4.8 | 39.4 | 15 | 5.1 | 40.5 | 31 | 5.1 | 40.4 | 64 |
| 21 | 11.5 | 41.1 | 6.8 | 40.0 | 21 | 6.9 | 41.6 | 41 | 8.6 | 41.4 | 104 |
| 25 | 4.5 | 45.9 | 4.6 | 44.2 | 13 | 4.4 | 45.8 | 24 | 4.3 | 45.1 | 48 |
| 29 | 5.3 | 45.7 | 5.0 | 44.9 | 14 | 4.4 | 47.2 | 23 | 5.5 | 46.5 | 60 |
| 33 | 4.9 | 49.1 | 4.6 | 47.7 | 12 | 4.4 | 49.5 | 22 | 4.3 | 48.7 | 44 |
| 37 | 4.4 | 51.0 | 4.4 | 49.4 | 11 | 4.4 | 51.0 | 22 | 4.2 | 50.1 | 42 |
| 41 | 5.9 | 53.1 | 6.3 | 51.1 | 15 | 5.8 | 53.2 | 27 | 6.2 | 52.0 | 60 |
| 45 | 5.8 | 54.0 | 5.7 | 52.5 | 14 | 5.6 | 54.1 | 26 | 6.1 | 52.2 | 58 |
| 49 | 5.5 | 56.2 | 5.4 | 54.5 | 12 | 6.3 | 55.6 | 28 | 6.3 | 54.4 | 58 |
| 53 | 5.2 | 56.9 | 5.0 | 55.6 | 11 | 5.2 | 57.1 | 23 | 5.8 | 55.5 | 52 |
| 57 | 5.4 | 58.2 | 5.1 | 56.4 | 11 | 5.6 | 58.0 | 24 | 5.2 | 56.8 | 46 |
| 61 | 4.8 | 59.5 | 4.8 | 57.9 | 10 | 4.8 | 59.3 | 20 | 4.9 | 58.1 | 42 |
| 65 | 4.6 | 59.9 | 5.0 | 58.5 | 11 | 4.6 | 61.0 | 19 | 5.0 | 58.6 | 42 |
| 69 | 5.1 | 61.6 | 6.0 | 59.3 | 13 | 5.7 | 62.1 | 23 | 6.1 | 58.2 | 53 |
| 73 | 4.9 | 62.8 | 5.4 | 60.2 | 11 | 5.1 | 62.2 | 20 | 6.4 | 58.0 | 55 |
| 77 | 5.0 | 63.3 | 5.4 | 61.0 | 11 | 6.2 | 61.9 | 25 | 7.8 | 55.4 | 71 |
| 81 | 4.6 | 62.2 | 4.9 | 60.3 | 10 | 5.8 | 60.4 | 24 | 7.3 | 51.6 | 70 |
| 85 | 4.9 | 61.1 | 5.4 | 58.6 | 11 | 7.7 | 58.8 | 33 | 8.6 | 48.7 | 89 |
| 89 | 2.6 | 60.0 | 2.7 | 58.0 | 6 | 3.4 | 54.4 | 16 | 3.2 | 45.8 | 35 |
| 93 | 5.8 | 57.4 | 7.1 | 56.3 | 16 | 9.7 | 50.9 | 47 | 8.5 | 43.7 | 97 |
| 97 | 6.0 | 55.7 | 7.8 | 52.7 | 18 | 10.4 | 47.1 | 55 | 8.6 | 40.2 | 106 |
| 99 | 6.0 | 56.1 | 8.4 | 53.3 | 20 | 10.1 | 46.1 | 55 | 8.0 | 40.1 | 100 |
| 101 | 5.4 | 55.5 | 9.2 | 52.5 | 22 | 10.7 | 42.8 | 62 | 8.0 | 39.9 | 100 |
| 104 | 5.9 | 55.3 | 8.7 | 49.0 | 22 | 10.7 | 41.5 | 64 | 8.0 | 38.0 | 106 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 6.5 | 28.1 | 6.3 | 28.0 | 30 | 6.3 | 28.3 | 58 | 5.5 | 28.3 | 102 |
| 14-52 | 5.8 | 48.5 | 5.3 | 47.1 | 14 | 5.3 | 48.7 | 27 | 5.6 | 47.9 | 60 |
| 53-104 | 5.1 | 59.0 | 6.1 | 56.6 | 14 | 7.0 | 54.9 | 34 | 6.8 | 49.9 | 71 |

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

APPENDIX M
INGREDIENTS, NUTRIENT COMPOSITION,
AND CONTAMINANT LEVELS
IN NIH-07 RAT AND MOUSE RATION

| | | |
|-----------------|---|------------|
| TABLE M1 | Ingredients of NIH-07 Rat and Mouse Ration | 320 |
| TABLE M2 | Vitamins and Minerals in NIH-07 Rat and Mouse Ration | 320 |
| TABLE M3 | Nutrient Composition of NIH-07 Rat and Mouse Ration | 321 |
| TABLE M4 | Contaminant Levels in NIH-07 Rat and Mouse Ration | 322 |

TABLE M1
Ingredients of NIH-07 Rat and Mouse Ration^a

| Ingredients ^b | Percent by Weight |
|--|-------------------|
| Ground #2 yellow shelled corn | 24.50 |
| Ground hard winter wheat | 23.00 |
| Soybean meal (49% protein) | 12.00 |
| Fish meal (60% protein) | 10.00 |
| Wheat middlings | 10.00 |
| Dried skim milk | 5.00 |
| Alfalfa meal (dehydrated, 17% protein) | 4.00 |
| Corn gluten meal (60% protein) | 3.00 |
| Soy oil | 2.50 |
| Dried brewer's yeast | 2.00 |
| Dry molasses | 1.50 |
| Dicalcium phosphate | 1.25 |
| Ground limestone | 0.50 |
| Salt | 0.50 |
| Premixes (vitamin and mineral) | 0.25 |

^a NCI, 1976; NIH, 1978

^b Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE M2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration^a

| | Amount | Source |
|---|---------------|---|
| Vitamins | | |
| A | 5,500,000 IU | Stabilized vitamin A palmitate or acetate |
| D ₃ | 4,600,000 IU | D-activated animal sterol |
| K ₃ | 2.8 g | Menadione |
| <i>d</i> - α -Tocopheryl acetate | 20,000 IU | |
| Choline | 560.0 g | Choline chloride |
| Folic acid | 2.2 g | |
| Niacin | 30.0 g | |
| <i>d</i> -Pantothenic acid | 18.0 g | <i>d</i> -Calcium pantothenate |
| Riboflavin | 3.4 g | |
| Thiamine | 10.0 g | Thiamine mononitrate |
| B ₁₂ | 4,000 μ g | |
| Pyridoxine | 1.7 g | Pyridoxine hydrochloride |
| Biotin | 140.0 mg | <i>d</i> -Biotin |
| Minerals | | |
| Iron | 120.0 g | Iron sulfate |
| Manganese | 60.0 g | Manganous oxide |
| Zinc | 16.0 g | Zinc oxide |
| Copper | 4.0 g | Copper sulfate |
| Iodine | 1.4 g | Calcium iodate |
| Cobalt | 0.4 g | Cobalt carbonate |

^a Per ton (2,000 lb) of finished product

TABLE M3
Nutrient Composition of NIH-07 Rat and Mouse Ration

| Nutrient | Mean \pm Standard Deviation | Range | Number of Samples |
|--|-------------------------------|----------------|-------------------|
| Protein (% by weight) | 23.45 \pm 0.49 | 22.3) 24.3 | 26 |
| Crude fat (% by weight) | 5.34 \pm 0.18 | 5.00) 5.90 | 26 |
| Crude fiber (% by weight) | 3.32 \pm 0.32 | 2.60) 4.30 | 26 |
| Ash (% by weight) | 6.42 \pm 0.21 | 5.94) 6.81 | 26 |
| Amino Acids (% of total diet) | | | |
| Arginine | 1.273 \pm 0.083 | 1.100) 1.390 | 12 |
| Cystine | 0.307 \pm 0.068 | 0.181) 0.400 | 12 |
| Glycine | 1.152 \pm 0.051 | 1.060) 1.220 | 12 |
| Histidine | 0.581 \pm 0.029 | 0.531) 0.630 | 12 |
| Isoleucine | 0.913 \pm 0.034 | 0.867) 0.965 | 12 |
| Leucine | 1.969 \pm 0.053 | 1.850) 2.040 | 12 |
| Lysine | 1.269 \pm 0.050 | 1.200) 1.370 | 12 |
| Methionine | 0.436 \pm 0.104 | 0.306) 0.699 | 12 |
| Phenylalanine | 0.999 \pm 0.114 | 0.665) 1.110 | 12 |
| Threonine | 0.899 \pm 0.059 | 0.824) 0.985 | 12 |
| Tryptophan | 0.216 \pm 0.146 | 0.107) 0.671 | 12 |
| Tyrosine | 0.690 \pm 0.091 | 0.564) 0.794 | 12 |
| Valine | 1.079 \pm 0.057 | 0.962) 1.170 | 12 |
| Essential Fatty Acids (% of total diet) | | | |
| Linoleic | 2.389 \pm 0.223 | 1.830) 2.570 | 11 |
| Linolenic | 0.273 \pm 0.034 | 0.210) 0.320 | 11 |
| Vitamins | | | |
| Vitamin A (IU/kg) | 6,681 \pm 1,265 | 5,280) 11,450 | 26 |
| Vitamin D (IU/kg) | 4,450 \pm 1,382 | 3,000) 6,300 | 4 |
| α -Tocopherol (ppm) | 35.24 \pm 8.58 | 22.5) 48.9 | 12 |
| Thiamine (ppm) | 17.27 \pm 2.14 | 13.0) 22.0 | 26 |
| Riboflavin (ppm) | 7.78 \pm 0.899 | 6.10) 9.00 | 12 |
| Niacin (ppm) | 98.73 \pm 23.21 | 65.0) 150.0 | 12 |
| Pantothenic acid (ppm) | 32.94 \pm 8.92 | 23.0) 59.2 | 12 |
| Pyridoxine (ppm) | 9.28 \pm 2.49 | 5.60) 14.0 | 12 |
| Folic acid (ppm) | 2.56 \pm 0.70 | 1.80) 3.70 | 12 |
| Biotin (ppm) | 0.265 \pm 0.046 | 0.190) 0.354 | 12 |
| Vitamin B ₁₂ (ppb) | 41.6 \pm 18.6 | 10.6) 65.0 | 12 |
| Choline (ppm) | 2,955 \pm 382 | 2,300) 3,430 | 11 |
| Minerals | | | |
| Calcium (%) | 1.16 \pm 0.05 | 1.09) 1.28 | 26 |
| Phosphorus (%) | 0.92 \pm 0.05 | 0.760) 1.00 | 26 |
| Potassium (%) | 0.886 \pm 0.059 | 0.772) 0.971 | 10 |
| Chloride (%) | 0.531 \pm 0.082 | 0.380) 0.635 | 10 |
| Sodium (%) | 0.316 \pm 0.031 | 0.258) 0.370 | 12 |
| Magnesium (%) | 0.165 \pm 0.010 | 0.148) 0.180 | 12 |
| Sulfur (%) | 0.266 \pm 0.060 | 0.208) 0.420 | 11 |
| Iron (ppm) | 348.0 \pm 83.7 | 255.0) 523.0 | 12 |
| Manganese (ppm) | 93.27 \pm 5.62 | 81.7) 102.0 | 12 |
| Zinc (ppm) | 59.42 \pm 9.73 | 46.1) 81.6 | 12 |
| Copper (ppm) | 11.63 \pm 2.46 | 8.09) 15.4 | 12 |
| Iodine (ppm) | 3.49 \pm 1.14 | 1.52) 5.83 | 11 |
| Chromium (ppm) | 1.57 \pm 0.53 | 0.60) 2.09 | 12 |
| Cobalt (ppm) | 0.81 \pm 0.27 | 0.49) 1.23 | 8 |

TABLE M4
Contaminant Levels in NIH-07 Rat and Mouse Ration^a

| | Mean ± Standard Deviation ^b | Range | Number of Samples |
|---|---|-----------------|-------------------|
| Contaminants | | | |
| Arsenic (ppm) | 0.49 ± 0.16 | 0.10) 0.70 | 26 |
| Cadmium (ppm) | 0.13 ± 0.07 | 0.04) 0.20 | 26 |
| Lead (ppm) | 0.36 ± 0.24 | 0.10) 1.00 | 26 |
| Mercury (ppm) ^c | <0.02 | 0.02) 0.03 | 26 |
| Selenium (ppm) | 0.32 ± 0.10 | 0.05) 0.40 | 26 |
| Aflatoxins (ppb) | <5.0 | | 26 |
| Nitrate nitrogen (ppm) ^d | 7.78 ± 3.83 | 2.90) 17.0 | 26 |
| Nitrite nitrogen (ppm) ^d | 0.18 ± 0.12 | 0.10) 0.50 | 26 |
| BHA (ppm) ^e | 2.46 ± 4.04 | 1.0) 20.0 | 26 |
| BHT (ppm) ^e | 1.35 ± 0.84 | 1.0) 5.0 | 26 |
| Aerobic plate count (CFU/g) | 95,542 ± 158,814 | 6,500) 710,000 | 26 |
| Coliform (MPN/g) | 3.1 ± 0.3 | 3) 4 | 26 |
| <i>Escherichia coli</i> (MPN/g) | <3 | | 26 |
| <i>Salmonella</i> (MPN/g) | Negative | | 26 |
| Total nitrosoamines (ppb) ^f | 7.87 ± 1.92 | 4.7) 11.4 | 26 |
| N-Nitrosodimethylamine (ppb) ^f | 5.73 ± 1.31 | 2.9) 8.2 | 26 |
| N-Nitrosopyrrolidine (ppb) ^f | 2.14 ± 1.26 | 1.0) 6.0 | 26 |
| Pesticides (ppm) | | | |
| α-BHC | <0.01 | | 26 |
| β-BHC | <0.02 | | 26 |
| γ-BHC | <0.01 | | 26 |
| δ-BHC | <0.01 | | 26 |
| Heptachlor | <0.01 | | 26 |
| Aldrin | <0.01 | | 26 |
| Heptachlor epoxide | <0.01 | | 26 |
| DDE | <0.01 | | 26 |
| DDD | <0.01 | | 26 |
| DDT | <0.01 | | 26 |
| HCB | <0.01 | | 26 |
| Mirex | <0.01 | | 26 |
| Methoxychlor | <0.05 | | 26 |
| Dieldrin | <0.01 | | 26 |
| Endrin | <0.01 | | 26 |
| Telodrin | <0.01 | | 26 |
| Chlordane | <0.05 | | 26 |
| Toxaphene | <0.10 | | 26 |
| Estimated PCBs | <0.20 | | 26 |
| Ronnel | <0.01 | | 26 |
| Ethion | <0.02 | | 26 |
| Trithion | <0.05 | | 26 |
| Diazinon | <0.10 | | 26 |
| Methyl parathion | <0.02 | | 26 |
| Ethyl parathion | <0.02 | | 26 |
| Malathion | 0.24 ± 0.23 | 0.05) 0.97 | 26 |
| Endosulfan I | <0.01 | | 26 |
| Endosulfan II | <0.01 | | 26 |
| Endosulfan sulfate | <0.03 | | 26 |

^a CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride

^b For values less than the limit of detection, the detection limit is given as the mean.

^c All values except for the lots milled November and December 1991 were less than the detection limit. The detection limit is given as the mean.

^d Sources of contamination: alfalfa, grains, and fish meal

^e Sources of contamination: soy oil and fish meal

^f All values were corrected for percent recovery.

APPENDIX N

SENTINEL ANIMAL PROGRAM

| | | |
|-----------------|---|------------|
| METHODS | | 324 |
| TABLE N1 | Murine Virus Antibody Determinations for Rats and Mice | |
| | in the 13-Week and 2-Year Studies of Pyridine | 327 |

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test

Time of Analysis

F344/N RATS

13-Week Study

ELISA

| | |
|---|-------------------|
| PVM (pneumonia virus of mice) | Study termination |
| RCV/SDA (rat coronavirus/ sialodacryoadenitis) | Study termination |
| Sendai | Study termination |

Hemagglutination Inhibition

| | |
|--------------------------|-------------------|
| H-1 (Toolan's H-1 virus) | Study termination |
| KRV (Kilham rat virus) | Study termination |

2-Year Study

ELISA

| | |
|-------------------------------|---|
| <i>Mycoplasma arthritidis</i> | Study termination |
| <i>Mycoplasma pulmonis</i> | Study termination |
| PVM | 6, 12, 16, 18, and 19 months, study termination |
| RCV/SDA | 6, 12, 16, 18, and 19 months, study termination |
| Sendai | 6, 12, 16, 18, and 19 months, study termination |

Immunofluorescence Assay

| | |
|------------|-------------------|
| Parvovirus | 6 months |
| RCV/SDA | Study termination |
| Sendai | 12 months |

Hemagglutination Inhibition

| | |
|-----|---|
| H-1 | 6, 12, 16, 18, and 19 months, study termination |
| KRV | 6, 12, 16, 18, and 19 months, study termination |

WISTAR RATS**13-Week Study**

ELISA

PVM

Study termination

RCV/SDA

Study termination

Sendai

Study termination

Hemagglutination Inhibition

H-1

Study termination

KRV

Study termination

2-Year Study

ELISA

M. arthritidis

6 months, study termination

M. pulmonis

6 months, study termination

PVM

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

RCV/SDA

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

Sendai

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

Immunofluorescence Assay

Parvovirus

3 months, study termination

RCV/SDA

Study termination

Hemagglutination Inhibition

H-1

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

KRV

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

MICE**13-Week Study**

ELISA

Ectromelia virus

Study termination

GDVII (mouse encephalomyelitis virus)

Study termination

LCM (lymphocytic choriomeningitis virus)

Study termination

MHV (mouse hepatitis virus)

Study termination

PVM

Study termination

Reovirus 3

Study termination

Sendai

Study termination

Immunofluorescence Assay

EDIM (epizootic diarrhea of infant mice)

Study termination

Mouse adenoma virus

Study termination

MVM (minute virus of mice)

Study termination

Hemagglutination Inhibition

K (papovavirus)

Study termination

Polyoma virus

Study termination

MICE (continued)**2-Year Study**

ELISA

| | |
|------------------------|---|
| Ectromelia virus | 6, 12, and 18 months, study termination |
| EDIM | 6, 12, and 18 months, study termination |
| GDVII | 6, 12, and 18 months, study termination |
| LCM | 6, 12, and 18 months, study termination |
| Mouse adenoma virus-FL | 6, 12, and 18 months, study termination |
| MHV | 6, 12, and 18 months, study termination |
| <i>M. arthritidis</i> | Study termination |
| <i>M. pulmonis</i> | Study termination |
| PVM | 6, 12, and 18 months, study termination |
| Reovirus 3 | 6, 12, and 18 months, study termination |
| Sendai | 6, 12, and 18 months, study termination |

Immunofluorescence Assay

| | |
|-------|------------------------------|
| GDVII | 12 months |
| MHV | 12 months, study termination |

Hemagglutination Inhibition

| | |
|---------------|---|
| K | 6, 12, and 18 months, study termination |
| MVM | 6, 12, and 18 months, study termination |
| Polyoma virus | 6, 12, and 18 months, study termination |

Results of serology tests are presented in Table N1.

TABLE N1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Studies of Pyridine

| Interval | Incidence of Antibody in Sentinel Animals | Positive Serologic Reaction for |
|------------------------|--|------------------------------------|
| 13-Week Studies | | |
| F344/N Rats | | |
| Study termination | 0/10 | None positive |
| Wistar Rats | | |
| Study termination | 0/5 | None positive |
| Mice | | |
| Study termination | 0/10 | None positive |
| 2-Year Studies | | |
| F344/N Rats | | |
| 6 Months | 1/10 | Parvovirus |
| | 1/10 | H-1 |
| 12 Months | 0/10 | None positive |
| 16 Months | 0/1 | None positive |
| 18 Months | 0/8 | None positive |
| 19 Months | 0/1 | None positive |
| Study termination | 6/16 ^a | <i>M. arthritidis</i> |
| Wistar Rats | | |
| 1 Week | 0/8 | None positive |
| 3 Months | 1/2 | Parvovirus |
| | 1/2 | H-1 |
| 5 Months | 0/1 | None positive |
| 6 Months | 0/6 | None positive |
| 12 Months | 0/5 | None positive |
| 14 Months | 0/1 | None positive |
| 18 Months | 0/5 | None positive |
| Study termination | 0/10 | None positive |
| Mice | | |
| 6 Months | 0/10 | None positive |
| 12 Months | 0/8 | None positive |
| 18 Months | 0/8 | None positive |
| Study termination | 0/10 | None positive |

^a Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. There were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered false positives.

